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A Symposium:
Systemic Hypertension:
Contribution of Trandolapril, a
New Angiotensin-Converting
Enzyme Inhibitor, Toward Patient
Protection

GUEST EDITORS:

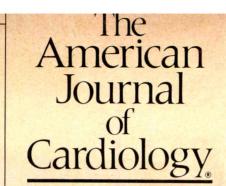
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Introduction

John H. Laragh, MD and Giuseppe Mancia, MD

igh blood pressure is the leading single risk factor predisposing to premature sickness and death. It is the major factor predisposing to congestive heart failure, heart attack, stroke, and kidney failure, which collectively comprise the leading cause of all sickness and death.

Some 25 years ago, an explosion in our knowledge about high blood pressure began. At that time, it was established by the U.S. Veterans Administration Study that if you reduce blood pressure effectively by drug therapy, you can protect patients from stroke and other morbid events such as congestive heart failure and renal failure, but not from a heart attack. Even today there is still doubt about whether antihypertensive therapy can protect from subsequent coronary events, which are, by far, the major morbid burden and the

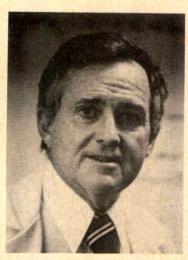
major cause of premature mortality in hypertensive patients.

The significant benefits of antihypertensive therapy have been abundantly verified in clinical trials, using older medications and involving a diureticbased regimen in which agents such as B blockers and other, older drugs, are added to a diuretic to achieve the desired blood pressure reduction. In this regard, it has remained possible that the types of antihypertensive agents used might explain the failure to achieve full cardioprotection. Thus, as knowledge has grown in the past 25 years, we are becoming increasingly aware, with the development of more and more specific drugs with a diversity of types of action, that lowering the blood pressure itself may not be enough, or may not even be the primary goal. It now seems that our ultimate goal is not to control the blood pressure level per se, but to lower it in a manner that will eliminate or reduce those attendant consequences that cause premature sickness and death—i.e., mainly coronary artery disease and its expressions.

In parallel, over the past 25 years there has also been an explosion in drug development that has

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produced 2 new major classes of pharmaceutical agents that theoretically might have greater promise for producing more cardioprotection with reduction in premature morbidity and mortality to rates seen in normotensive people. One of these 2 classes are the calcium antagonists, which modify vascular tone and cardiac performance by reducing cytosolic calcium levels. These agents have been shown to have an antiatherogenic effect in both animal and human studies. To date, however, controlled trials have been limited and convincing evidence of protection from angiographic coronary artery disease remains undocumented, although beneficial effects on coronary artery disease have been shown in preliminary reports using either verapamil or diltiazem (MDPIT and DAVIT II studies). Also, prevention or regression of left ventricular hypertrophy with these drugs has been demonstrated in some studies. More work is needed to verify or refute these preliminary impressions. It seems possible that longer-acting dihydropyridine calcium antagonists, which do not activate the sympathetic nervous system, such as amlodipine or lacidipine, could have special promise for achieving significant cardioprotection.

A second class of drugs developed over the past 25 years, the converting enzyme inhibitors, holds special promise for cardioprotection. No clinical trials in essential hypertension are available. However, these drugs are promising because in patients with congestive heart failure (SOLVD and SAVE Studies) and in those who have already had a myocardial infarction, converting enzyme inhibitor therapy has in fact been shown to be superior to diuretic therapy for preventing heart attacks. Although these findings are encouraging, only prospective trials can finally establish the true cardioprotective benefit of converting enzyme inhibition over conventional therapy in patients with high blood pressure.

Meanwhile, in the absence of definitive information, extrapolation from another large body of accumulating evidence suggests that containment of the renin-angiotensin system may be an attractive strategy for achieving correction of the increased morbidity and mortality associated with the presence of high blood pressure. As recently as 25 years ago, nobody in the world thought that plasma renin had anything to do with high blood pressure. Now we know that the renin-angiotensinaldosterone system is a major servo-control for the simultaneous normal regulation of sodium balance and arterial blood pressure. We also know that specific derangements of the renin-angiotensin system associated with inappropriately or absolutely increased levels of plasma renin in the blood can play a role in causing or sustaining a hypertensive condition. Furthermore, excesses of plasma renin-angiotensin in both humans and experimental animals have been associated with more clinical coronary events and with changes in the myocardium resembling acute myocardial infarction.1

In humans, Brunner et al² first described a powerful retrospective association between plasma renin levels and myocardial infarction and stroke, and protection from these events in patients with low plasma renin levels despite their greater age and even higher systemic blood pressure levels. Similar results have recently been reported in a prospective controlled trial of patients with mild hypertension.3 Further, animal studies describe lesions in the heart after mildly pressor infusions of renin or angiotensin that resemble an early human myocardial infarction (Laragh and Sealey, 1 Gavras et al.4 Giacomelli et al⁵).

Evidence has also emerged suggesting that other pathophysiologic changes associated with excessive plasma renin activity may increase the risk of morbid events in hypertensive patients. Thus, it has been found that white males, who suffer most of the heart attacks, are the only group in whom plasma renin levels fail to decline over age 50.6 Another study has shown that diurnal variability of the blood pressure as revealed by 24-hour monitoring is closely associated with the plasma renin level.⁷ The factors responsible for blood pressure variability need to be further investigated, and it is likely that not only the renin-angiotensin system, but also autonomic cardiovascular control and other mechanisms, are involved.8 The issue is important, however, because for any given level of 24-hour mean blood pressure, blood pressure variability has been shown to correlate with hypertensive target organ damage.9 This correlation has been shown both in cross-sectional and in follow-up studies, suggesting that the adverse consequences of hypertension on the cardiovascular system may depend both on prevailing blood pressure values and on the magnitude (and possibly the rate) of blood pressure variations. This would imply that antihypertensive drugs should be assessed not only for their ability to lower blood pressure means, but also for their ability to lower blood pressure variability.

Accordingly, by extrapolation, containment of inappropriate renin-angiotensin system activity in hypertensive patients provides a theoretically attractive strategy for protection of attendant cardiovascular morbidity and mortality. Also, what may be relevant to this strategy is the fact that trandolopril, a compound developed by the sponsors of this symposium, is a converting enzyme inhibitor with a very long duration of action, making it especially suitable for once-a-day use to achieve a continuous, smoother suppression of the renin system. We are pleased to organize and arrange this symposium to probe some of these possibilities and their implications for patient care.

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Clinical Value of Blood Pressure Measurements: Focus on Ambulatory Blood Pressures

Stefano Omboni, MD, Alessandra Frattola, MD, Gianfranco Parati, MD, Antonella Ravogli, MD, and Giuseppe Mancia, MD

Because clinic blood pressure values are compromised by 2 major limitations—the alerting reaction to clinic measurements and the spontaneous blood pressure variability—they have only a limited correlation with average 24-hour blood pressure values. Whether the latter should be employed routinely in substitution for, or in addition to, traditional blood pressure measurements has not yet been determined, however. To date, average 24-hour blood pressure values have been shown to correlate more closely than clinic blood pressure values with the organ damage of hypertension. A correlation with organ damage has been shown also for a number of blood pressure values within the 24 hours. Nevertheless, the clinical importance of 24-hour blood pressure and blood pressure variability has never been confirmed by prospective controlled studies. This information needs to be obtained before this approach is routinely employed in the clinical practice.

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large number of epidemiologic studies have shown that although systemic blood pressure values, as determined by the traditional method of measurement, i.e., by sphygmomanometer in the clinical setting, is related to the incidence of cardiovascular morbidity and mortality, the relation is far from close. One explanation for this may be genetic differences in individual susceptibility to the cardiovascular damage produced by a blood pressure elevation. It can also be explained by the fact that other cardiovascular risk factors (dyslipidemia, smoking, diabetes, stress, etc.) obscure the basic relationship between blood pressure and cardiovascular complications.

However, a third possibility (not exclusive of the previous ones) is that clinic blood pressure measurements are to some extent inadequate in reflecting the real life daily blood pressure values due to (1) the limited ability of sphygmomanometry to detect systolic and diastolic blood pressure precisely, particularly in overweight and elderly patients; (2) the patient's "alerting reaction," inherent to clinic blood pressure measurements, which variably overestimates initial blood pressure and underestimates the antihypertensive effect of treatment in many patients (so-called "white coat" hypertension),^{2,3} and (3) the low number of values provided by traditional sphygmomanometry with respect to the hundreds of thousands of values occurring over the 24 hours.

In fact, this is the most serious limitation, because blood pressure is so highly variable during the 24 hours that in most subjects peak-to-trough differences over this time interval are greater than 50 mm Hg.^{4,5} Thus, it is not surprising that clinic blood pressure has invariably been found to be higher than 24-hour or day-time blood pressure means^{6–8} and that these values have always been shown to have only a limited correlation with each other. This is exemplified in Figure 1, which refers to subjects classified into 4 groups according to the World Health Organization (WHO) criteria for definition of normotension, borderline hyperten-

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TABLE I BP and Organ Damage in Hypertension

Ambulatory blood pressure correlates more closely than clinic blood pressure to:

- Left ventricular mass
- · Impaired systolic function
- Impaired diastolic function
- Albuminuria
- Cerebral Jacunae

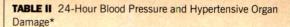
(as shown by nuclear magnetic resonance)

BP = blood pressure

sion, and mild and severe hypertension.9 The points represent the 24-hour mean blood pressure (intra-arterial recording) in each individual, and it is clear that their values overlap markedly between the groups. This overlap gives a measure of the lack of correspondence between the classification of blood pressure values employed traditionally and the actual 24-hour prevailing blood pressure regimens.8

The above considerations raise the question whether clinic blood pressure should be replaced or complemented on a routine basis by data obtained via ambulatory blood pressure measurement—i.e., whether ambulatory blood pressure measurement improves the diagnosis of hypertension, the prediction of the risk, and the estimation of the need of treatment. In the opinion of the authors this question cannot yet be given a positive answer because (1) conclusive evidence is not yet available on ambulatory blood pressure normalcy (preventing any reliable conclusion as to whether the ambulatory blood pressure values are within, above, or below the normal range) and (2) the only evidence on the prognostic value of ambulatory blood pressure comes from uncontrolled follow-up data. No controlled prospective study is available to prove conclusively that ambulatory blood pressure values are related to the incidence of cardiovascular complications and that their predictive power adds to the prognosis offered by clinic blood pressure measurement.3

However, these negative considerations are tempered by several promising findings. A large number of studies have shown that the prognosis of hypertensive organ damage is more closely related to 24-hour or daytime ambulatory blood pressure mean than to clinic blood pressure values. 10 This is the case when the damage is quantified by a comprehensive score, taking into account the history, the physical examination, and the laboratory examination of the hypertensive individual. 11,12 It is also the case when more precise estimates of the consequence of hypertension on various organ structures and functions are considered (Table I). 10,13-19



Work BP (left ventricular mass)

Exercise BP (left ventricular hypertrophy)

Morning BP rise (myocardial ischemia, infarction, sudden death)

Sleep BP (left ventricular mass)

BP variability (overall organ damage score)

BP = blood pressure.
*Direct correlation in all instances.

As shown in Table II, evidence is also available that the organ damage of hypertension is related to some blood pressure values occurring within the 24 hours (exercise blood pressure, work blood pressure, peak blood pressures, etc.).3 We have shown that the damage assessed by the comprehensive score is to some extent related to 24-hour blood pressure variability, i.e., in untreated hypertensive subjects having similar 24-hour mean blood pres-

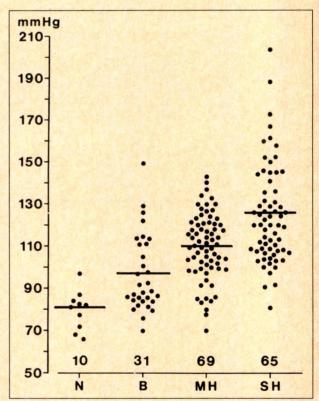


FIGURE 1. The 24-hour mean arterial pressure values in 175 subjects who underwent intra-arterial monitoring. The subjects were subdivided into a normotensive group (N), a group with borderline hypertension (B), a group with moderate essential hypertension (MH), and a group with se vere essential hypertension (SH), according to World Health Organization criteria for clinic diastolic blood pressure (<90 mm Hg = normotensive, >90 and <95 mm Hg = borderline hypertensive, >95 and <110 mm

Hg = moderately hypertensive, and >110 mm

Hg = severely hypertensive). The bars show the average 24-hour values for each group. (Adapted with permission from J Cardiovasc Pharmacol.8)

TABLE III Multiple Regression Analysis and Blood Pressure **Parameters**

Initial Evaluation	Beta
Clinic MAP	0.17
24-hour MAP	0.18
24-hour MAP SD	0.23 p < 0.05
TOD	0.30 p < 0.05
Follow-up clinic MAP	0.32 p < 0.01

Analysis was between clinic blood pressure (BP), 24-hour BP \pm standard deviation at initial evaluation, and target organ damage and clinic BP at follow-up (7.4 \pm 2.1 years \pm SE); n = 75. r = 0.55 multiple correlation coefficient; Beta = standardized regression coefficient. MAP = mean arterial pressure; SD = standard deviation; TOD = target organ damage.

damage

sure values (intra-arterial recording), the damage tends to be greater when the standard deviation of the 24-hour values is greater, and vice versa. 12 This allows speculation that hypertensive organ damage depends both on the mean blood pressure level and on the extent of the blood pressure variations. Of course, caution should be employed in interpreting cross-sectional relationships in a cause-effect fashion, and also the clinical importance of blood pressure variability needs to be confirmed by longitudinal observations.

This was done in 73 hypertensive patients (out of the 108 in the above cross-sectional study) who were reexamined after 7.5 years of variably effective antihypertensive treatment. During this period the organ damage score remained unchanged or was reduced in 55.7% patients, whereas in the remaining 44.3% it was increased. On multivariate analysis the actual organ damage was significantly related to the pretreatment organ damage and the

clinic blood pressure values obtained during the treatment phase. Out of the hemodynamic data available at the pretreatment examination (clinic blood pressure, 24-hour intra-arterial mean blood pressure, 24-hour blood pressure standard deviation), only 24-hour blood pressure standard deviation showed a significant relationship with the actual organ damage (Table III).

With key evidence lacking and only promising information available, what might be the most appropriate clinical use of ambulatory blood pressure monitoring? In our opinion, clinic blood pressure measurements should remain the reference value for diagnosing hypertension and deciding on treatment in most patients. Clinic blood pressure measurements should remain the reference value also for the evaluation of antihypertensive treatment, except perhaps when a persistent marked alerting reaction raises the possibility that the real effect of treatment is obscured. On the other hand, ambulatory blood pressure monitoring should be used for clinical studies on antihypertensive drugs to ensure that the treatments employed are capable of causing what common sense suggests to be appropriate, i.e., an even reduction in blood pressure throughout the 24 hours.

Considering that (1) night-time blood pressure values are higher in hypertensive than in normotensive subjects (Figure 2)3 and (2) in hypertensive subjects organ damage is related not only to the elevated blood pressure values occurring during the day but also to the reduced values occurring during the night,8 it seems reasonable to suggest

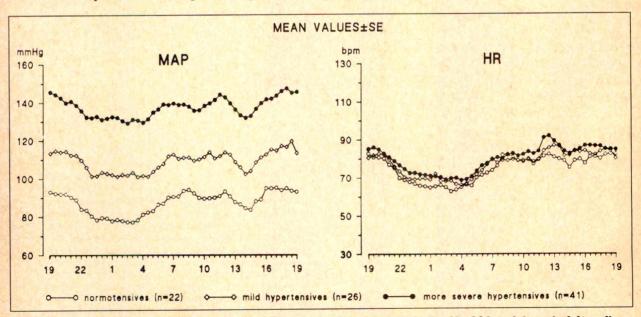


FIGURE 2. Hourly mean arterial pressure (MAP) and heart rate (HR) averages obtained by 24-hour intra-arterial monitoring in a group of 22 normotensive subjects, in a group of 26 mild hypertensives and in a group of 41 subjects with severe hypertension. Data are shown as means \pm SE. (Adapted with permission from Hypertension.3)

that the goal of blood pressure reduction should include not only day-time but also night-time values. It is also reasonable to suggest that the blood pressure reduction induced by antihypertensive treatment should be associated with a proportional reduction in blood pressure variability. This cannot be easily studied by automatic blood pressure monitoring, which provides a minute fraction of the overall 24-hour blood pressure values and thus misses most of the blood pressure variations.²⁰ It can be studied, however, by beat-to-beat intraarterial monitoring. This was done in 51 patients in whom 24-hour intra-arterial blood pressure monitoring was performed before and after several weeks of antihypertensive treatment. It was shown that treatment reduced 24-hour blood pressure mean and within-half-hour standard deviation values (a variability mainly representative of shortlasting blood pressure changes). However, the among-half-hour blood pressure standard deviation (a more long-lasting variability reflecting the

TABLE IV Changes in Blood Pressure Variability with Treatment in 51 Hypertensive Patients

24-Hou	ır MAP	24-Hour MAP SD*	
ВТ	DT	ВТ	DT
113.0 ± 2.3†	95.2 ± 1.9	11.1 ± 0.4	11.4 ± 0.5

Data are means \pm SE. * = among-half-hour standard deviation; BT = before treatment; DT = during treatment. †p <0.01.

differences among-half-hour mean values) was unaffected (Table IV), indicating a less-than-optimal effect. Whether this is related to the less-than-expected benefits of antihypertensive treatment remains to be seen.

Finally, 4 further considerations are needed. One, available measuring devices have a limited accuracy when used in ambulatory conditions. This is the case also for most recent devices (Figure 3), 10,21 which means that technical progress toward greater accuracy is important. Two, technical

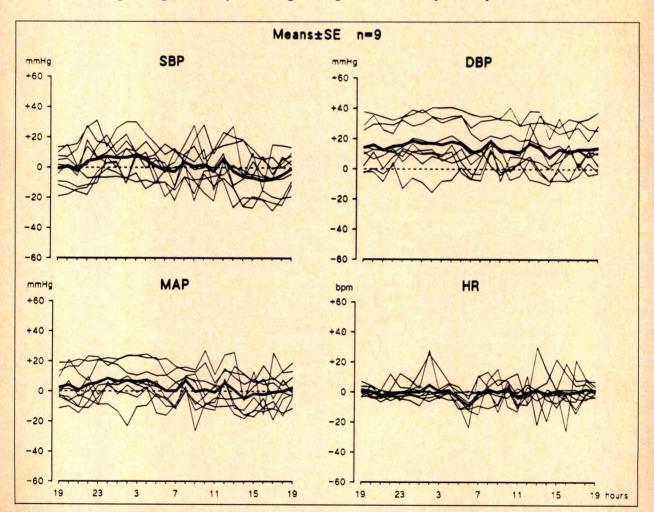


FIGURE 3. Hourly discrepancies between systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) obtained by Spacelabs devices and intra-arterially during a 24-hour period in 9 subjects. Data are shown for individual subjects (thin lines) and for the group as a whole (thick line). Dashed line refers to reference intra-arterial values. (Adapted from *Hypertension*.²¹)

progress should also be directed toward the availability of noninvasive devices capable of measuring beat-to-beat blood pressure values in order to estimate blood pressure variability.²² Three, ambulatory blood pressure normalcy should be defined by studies comparing clinic and ambulatory blood pressures in large randomly selected samples of a population. This is under way in Monza (the Pamela Study)²³ and in other European towns, which means that this particular problem may soon be resolved.

The final consideration concerns the prognostic value of ambulatory blood pressure. It is a widespread opinion that a prognostic study based on cardiovascular morbidity and mortality will have to be too large and prolonged to be feasible and that a surrogate endpoint will have to be chosen instead. This has been done in an Italian multicenter study, which aims at determining whether the regression of left ventricular hypertrophy induced by antihypertensive treatment with an angiotensin-converting enzyme (ACE) inhibitor and a diuretic is more closely predicted by the fall in ambulatory blood pressure than by the fall in clinic blood pressure. This will test the clinical relevance of ambulatory blood pressure on a hypertension-dependent alteration of undisputed prognostic value. 24,25

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After the Diagnosis of Systemic Hypertension, Is Risk Factor Management Important?

Peter Sleight, MD

In the hypertensive patient, the presence of other cardiovascular risk factors, particularly smoking, hypercholesterolemia, obesity, and diabetes, greatly influences the prognosis. In many patients, these other risk factors are linked, perhaps by adverse effects of pressure on endothelial function. The newer antihypertensive agents may have better effects on prognosis by ameliorating these other risk factors, as well as lowering pressure. We await trials to see if this promise is fulfilled.

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n the setting of a diagnosis of systemic hypertension, it is of particular importance that risk factors in addition to the absolute blood pressure (BP) levels in an individual patient be considered. This article will begin by consideration of this point, then briefly review the evidence in favor of intervention, and finally will review the impact of drug therapy on these risk factors.

RISK FACTOR ASSESSMENT

Population statistics show quite clearly the additive adverse effects of systemic hypertension, dietary cholesterol, and smoking—the major risk factors for cardiovascular disease in Western urbanized societies (Figure 1). As a result, hypertension alone is just one factor to be considered in the assessment of cardiovascular risk. Rather, current medical practice increasingly takes a holistic approach to a given patient and therefore tries to modify other risk factors at the same time as lowering BP.

The epidemiologic data also show a curvilinear relation between BP and cardiovascular risk, with a steeply increasing risk for systolic pressures ≥ 160 mm Hg. However, as MacMahon and colleagues² have clearly shown, the relation is linear when a doubling scale is used for risk (Figure 2). Note that there is no evidence for increased risk at very low pressures, i.e., there is no evidence of the so-called "J curve" when populations are considered. This is important in the difficult decision as to what level of BP warrants treatment. Too often, rules are set that are overly simplistic and that seek to define a level of BP that divides "normal" from "hypertension."

This approach is outdated. Consideration of Figure 2 clearly shows that the *proportional* decrease in risk is the same, whether the hypertensive patient in question moves from quintile 5 to 4 (Q5 to Q4) or from Q2 to Q1. Although this is true for proportional benefit, the *absolute* benefit is equally clearly greater for a one quintile decrease at the top of the line, provided that all other risk factors (apart from BP) are equal. But if the hypothetical

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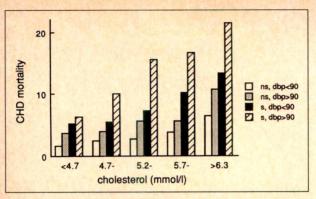


FIGURE 1. Age standardized coronary heart disease (CHD) mortality (6-year rate/1,000) by cholesterol quintile, by smoking status (ns = nonsmoking, s = smoking), by diastolic blood pressure (dbp) (< and >90 mm Hg) (recalculated from the Multiple Risk Factor Intervention Trial). The greater the number of risk factors, the higher is the mortality. (Reprinted with permission Eur Heart J.1)

patient who moves from Q5 to Q4 is at low additional cardiovascular risk, the benefit may be equal to, or even less than, that of a high risk patient (e.g., smoking, cholesterol) who moves from O2 to O1—a level (Q2) that we would not normally treat. This argues that we should consider the effects of lowering BP in high risk subjects with so-called "normal" BP.

Such an approach needs testing in trials, since the proponents of the J curve argue that this approach will be dangerous, particularly in patients with signs of cardiac ischemia.3,4 The argument is that if a coronary stenosis is present, then lowering diastolic BP too much will compromise myocardial blood flow. This sounds plausible but seems likely to prove false. Similar arguments were formerly presented for withholding treatment from hypertensive patients with stroke. Yet when this was tested in a trial,⁵ the actively treated patients did better than those on placebo. Similarly, data from the Beta-Blocker Pooling Project showed benefit for the active (versus control) treatment of patients with previous myocardial infarction (i.e., patients with a high likelihood of coronary stenoses) at diastolic pressures well below those at the inflection point of published J curves.6

This strategy of antihypertensive treatment depends implicitly on the MacMahon et al² analysis, which suggests that our definition of "normal" BP needs revision downward. I believe that most urban BPs are biologically abnormal (in exact parallel with "normal" cholesterol). In practice, there may be less benefit in treating persons with lower pressures, since the other risk factors are not present in isolation but are linked with systemic blood pressure levels in the same individual, as pointed out by Ferrannini et al⁷ and Reaven.⁸ For example, even smoking has been shown to be linked to insulin resistance and adverse lipid changes, which may partly explain the mechanisms underlying the risk from tobacco.9

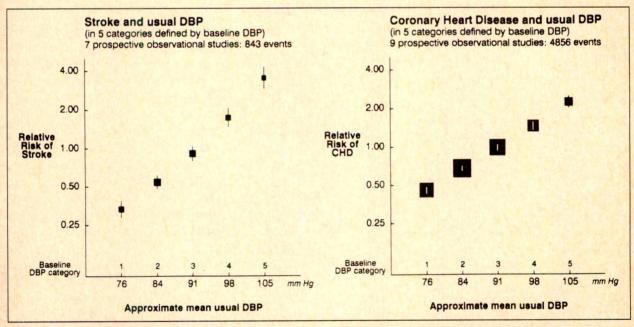


FIGURE 2. Relative risks of stroke and coronary heart disease (CHD). Estimates of the usual diastolic blood pressure (DBP) category are taken from the mean DBP values 4 years postbaseline in the Framingham study. Solid squares represent disease risk in each category, relative to risk in the whole population: sizes of squares are proportional to the number of events in each DBP category, and 95% confidence limits are indicated by vertical lines. (Reprinted with permission from Lancet.2)

SMOKING: EVIDENCE FOR INTERVENTION

Of all antihypertensive strategies, cessation of cigarette smoking has total support. The gains are particularly great in those with established coronary artery disease. For example, after a myocardial infarction, smoking cessation halves the risk for future cardiovascular events, 10 and statistically the benefit is seen quite quickly—within 1-2 years. This suggests that the mechanism of benefit is more related to thrombotic factors (e.g., decreased platelet adhesiveness and/or circulating fibrinogen) than to effects on the atheromatous plaque.

REVERSING LIPID ABNORMALITIES

Although the relation between serum cholesterol and cardiovascular mortality is now established beyond any doubt,1 the wisdom of intervening to lower cholesterol is increasingly questioned, except in those individuals with the highest levels. The reasons for this growing scepticism are probably several. One influential argument states that although cardiovascular mortality is lowered by interventions, whether dietary, behavioral, and/or pharmacologic, there has been no significant effect on total mortality. This statement is true, but omits the important proviso that the trials to date have been completely lacking in the statistical power required to address the question. Approximately 25,000 people have been randomized in these trials. Many were at relatively low risk, and in addition the degree of reduction in circulating cholesterol was also small. The reduction in total mortality that might have been expected from these trials has been calculated to be only 6% (Peto, R: Personal communication), because the majority of the small number of deaths were due to noncardiac causes, such as accident or trauma. The actual decline in mortality observed in these trials was a nonsignificant 3%, not significantly different from the 6% expected. Much has also been made of the just significant (p = 0.05) increase in noncardiac mortality from causes such as suicide, trauma, violence, and murder. These outcomes, for which it seems difficult to find any real connection, are not individually in any statistical excess. An hypothesis has been suggested by Engleberg¹¹ to the effect that lowered cell membrane cholesterol leads to reduction in serotonin (5-HT) receptor density, which is associated with decreased levels of brain serotonin, with the subsequent adverse effects on behavior. Publication of this hypothesis was followed by several letters pointing out the inherent

improbability of, and lack of supporting evidence for, this theory. 12,13

Finally, some trials, such as the recently published Finnish study,14 have reported strikingly adverse results, showing significant increases in both total and cardiovascular deaths following treatment to lower cholesterol. It should be noted that this latter trial was carried out on healthy middle-aged men with few cardiovascular risk factors; the numbers of deaths were consequently small and the risk of a chance negative result correspondingly large.

Opposed to these apparent arguments against an anticholesterolemic therapeutic approach must be set the overall benefit on cardiovascular mortality (more than 5 standard deviations difference. Peto, R: Personal communication). Consequently, it appears that the evidence in favor of intervening to lower lipids must be taken as compelling, particularly in the setting of hypertension; it is also very much more certain than the barely significant adverse evidence.

NEWER RISK FACTORS: INSULIN RESISTANCE. ENDOTHELIAL DYSFUNCTION, SMOOTH MUSCLE GROWTH FACTORS, ANGIOTENSIN

The importance of endothelial dysfunction has been highlighted in recent studies. 15,16 This important "endocrine organ" not only produces endothelium-derived relaxing factor (EDRF, thought to be nitrous oxide, NO) but also has many metabolic functions, including lipid regulation. Hypertension itself is associated with deficient production of EDRF in humans. This abnormality is exacerbated by sodium and mitigated by potassium in isolated vascular segments.17

Elsewhere in this supplement Alderman reports the recent evidence implicating abnormal regulation of the renin-angiotensin system as a risk factor.

EFFECTS OF BLOOD PRESSURE REDUCTION ON CARDIOVASCULAR RISK

Almost all of the antihypertensive trials have reported a large, approximately 40%, reduction in stroke. 18 This is very close to what might have been expected from the epidemiologic data on very long-term differences in BP.2 It is, therefore, surprising that this can be achieved in just 2-3 years of treatment, on average.

On the other hand, the reduction in coronary artery disease (CAD) as a result of lowering BP has generally been thought to be disappointing. However, an update of the 1990 Lancet publication by Collins et al¹⁸ that takes into account the results of the trials that have been published since the Lancet article (i.e., Systolic Hypertension in Elderly Patients [SHEP19], Swedish Trial in Old Patients, with hypertension [STOP],²⁰ and the Medical Research Council trial of treatment of hypertension in older adults²¹) shows a highly significant 16% reduction in CAD, which is only a little short of the 23% reduction expected from the epidemiologic data (Collins, R: Personal communication, 1992).

Note also that in the epidemiologic relation between hypertension and risk in the normal population, there are 5 times as many coronary as cerebral events (Figures 1 and 2), whereas in the published antihypertensive trials, coronary events still outnumber cerebrovascular accidents, but by only 2:1.18 Most of these events take place at relatively normal BP levels. Therefore, any strategy to lower this toll must consider reducing systemic blood pressure to lower than conventionally accepted levels in patients at high risk, once we are assured (by the newer trials) that this is free from risk and unacceptable side effects.

IMPACT OF RISK REDUCTION ON CHOICE OF **ANTIHYPERTENSIVE THERAPY**

The recent trials of antihypertensive treatment in elderly patients, such as the Medical Research Council and SHEP trials, have reinforced the message from the European Working Party on Hypertension in the Elderly (EWPHE) trial^{22,23} that thiazide diuretics appear to be the most effective agents so far subjected to large-scale testing. However, we should bear in mind that relatively short-term trials, particularly in the elderly (where adverse effects on serum lipids might be of less importance) may not be so applicable to the long-term effects, over quite possibly many decades of treatment, in younger hypertensive patients. In younger patients the adverse lipid and metabolic effects of thiazide diuretics have led to a gradual decrease in the use of these drugs.

The newer agents, particularly the calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors, have been shown to have more favorable effects on such well-validated risk factors as serum lipids, left ventricular hypertrophy, and insulin resistance. Quite rightly, the marketing of these newer agents has been based on the messages derived from these surrogate measures.

However, my experience of clinical trials has taught me that surrogate endpoints, like journalistic opinion polls, are not always reliable guides to true outcome. In my opinion, there is really no alternative to large-scale, long-term trials testing these newer antihypertensive agents against the older, well-established, and, importantly, cheaper agents, such as the thiazide diuretics. Until this is done, there will continue to be a great deal of confusion among clinicians, who are struggling to reconcile the often seductive marketing of these agents with the hard evidence from the recent trials showing benefit from thiazide treatment.24 Until we have equal evidence for the newer agents, there may well be a renaissance in the use of thiazide-based therapy. Fortunately, such trials are being planned.

Physicians treating hypertensive patients are increasingly aware of the need to treat other risk factors when the BP is raised. The next decade may see the treatment of so-called normal BP when other risk factors are present.

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Can the Genetic Factors Influence the Treatment of Systemic Hypertension? The Case of the Renin-Angiotensin-Aldosterone System

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The hereditary nature of familial hypertension has been clearly established by a number of clinical studies. About 30% of the blood pressure variance can be attributed to genetic factors. As a consequence, the relative risk for developing coronary artery disease or cardiovascular death is increased in patients with a family history of hypertension and cardiovascular disease. Patients with such familial history should be considered at the same risk as those who have independent epidemiologic risk factors. The development of molecular genetics allows establishment of a link between high blood pressure, intermediate phenotypes, and the genes involved in blood pressure regulation. Gene markers should be available in the near future that will help to identify patients predisposed to hypertension. The genes of the renin-angiotensin-aldosterone system are good examples of candidate genes whose products are known to participate in blood pressure regulation. The possible involvement of these genes in essential hypertension is critically analyzed.

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ver since blood pressure could first be reliably measured, many studies have been carried out on the population distribution and hereditary nature of hypertension. Blood pressure is a quantitative trait that varies continuously throughout the whole population and whose regulation is controlled by a variety of mechanisms that involve several genetic loci and environmental factors. However, little is known about the genes actually involved in human hypertension, about their respective importance in determining blood pressure level, or about their interaction with other genes and environmental components. Can these genetic factors influence management of the hypertensive patient? The answer to this question requires consideration of the respective contributions of genetic and environmental factors to blood pressure variance, the relative risk of developing hypertension, cardiovascular disease (CVD), or death in patients with family history of hypertension and/or CVD, and, finally, consideration of the several genes of the renin-angiotensin-aldosterone cascade, a major system involved in blood pressure regulation.

MECHANISMS OF BLOOD PRESSURE VARIANCE

A number of epidemiologic studies have shown that individual blood pressure levels result from both genetic predisposition and environmental factors. The heritable component of blood pressure has been documented in familial and in twin studies and in studies such as those performed in Montreal, where blood pressure levels were documented in families with natural and adopted children. 1 As shown in Table I, the evidence suggests that approximately 30% of the variance of blood pressure is attributable to genetic heritability and 50% to environmental influences.

The familial component of high blood pressure can also be estimated by self-questionnaire from hypertensive patients. Although recognized as hav-

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ing limited value,2 this approach allows screening of hypertensive patients with a putative family history of hypertension. Review of the Artemis data bank from the Hypertension Clinic of Hôpital Broussais showed that 13% of hypertensive patients reported at least 1 parent and 1 sibling with hypertension.3 Interestingly, the family history of hypertension was associated with a marked increase in the incidence of cardiovascular deaths in both parents before the age of 65 years, and also by an increase in the prevalence of cardiovascular accidents in both parents, again before the age of 65 years. High blood pressure was detected at a younger age in patients with a family history of hypertension than in patients without an apparent genetic component.

A positive family history of hypertension has a practical clinical application for identifying persons at high risk for hypertension. As reported by Williams et al⁴ in a Utah epidemiologic study, normotensive persons aged 20–49 years, ≥ 2 hypertensive first degree relatives and followed for 7 years had 4 times more risk for developing high blood pressure than persons without a family history of hypertension. In older adults, relative risk for high blood pressure depends less on a positive family history of hypertension, likely because of the more prominent role of environmental factors at this age. Therefore, the finding of a strong positive family history of hypertension, especially in a young hypertensive patient, should encourage physicians to search for high blood pressure in first degree relatives and to advocate strongly risk factor treatment.

RELATIVE RISK FOR DEVELOPING CORONARY ARTERY DISEASE OR CARDIOVASCULAR DEATH

Patients with family history of hypertension and/or cardiovascular disease: Although there have been a number of reports demonstrating familial clustering of individuals with coronary artery disease (CAD) and heart disease risk factors, there have been relatively few prospective studies relating the independent predictive strength of a positive family history of hypertension/CVD and the incidence of new cases of CVD. One of the earliest studies was performed by Cambien et al,5 who studied the relation between a familial history of hypertension and CVD versus the incidence of CVD. A cohort of 7,484 professional men, 43–54 years old, was followed for 6.5 years. The incidence of CVD was studied among those free of CVD at

TABLE I Mechanisms Implicated in Blood F	Pressure Variance
Genetic heritability	30%
Allelic effect on a single gene	
Gene-gene interactions	
Gene-environment interactions	
Environmental influences	50%
Cultural heritability	10%
Residual variance	10%

entry, in relation to a parental history of CVD and high blood pressure, obtained by self-questionnaire. The relative risk of developing CVD was 1.5 and 2.0 in presence of a paternal history of CVD or high blood pressure (after exclusion of the patients with hypertension), respectively. The presence of a paternal history of both CVD and hypertension increased the relative risk to 3.0. Maternal history of CVD or hypertension was not associated with a higher risk.

Other studies have shown that a family history of CVD was an independent predictor of cardiovascular mortality and morbidity. Barrett-Connor and Khaw⁶ showed in a 9-year follow-up of a community of 4.014 men and women, 40-79 years old, that in men, but not in women, a positive family history of heart attack was independently predictive of death from cardiovascular and ischemic heart disease. In this study, men < 60 years old had a 5-fold excess risk of cardiovascular death that was independent of all other risk factors.

Although most studies have concluded that family history is a risk factor for CVD, independent of other factors, it must be recognized that none can be considered conclusive. Indeed, a number of objections can be addressed to these reports, such as the weakness of self-reported data for CVD family history, inadequate in sample sizes, and unmeasured parameters that today are considered recognized risk factors (such as the cholesterol fractions in the Framingham study). Taking into consideration these limitations, it is interesting to note that in all studies but one,⁷ parental history appeared to be an independent risk factor for CAD, in spite of underreporting of parental CAD death. In the Framingham study, there was a possible genetic factor in CAD death, which seemed more frequent in persons who are otherwise at low risk for CAD.8 Similarly, Jorde and Williams9 concluded from their study in a Utah cohort that the differences in family history of CAD could not be explained by measured risk variables and that family history was itself a risk factor for incidence of CAD. The other factors involved for determining familial CAD might be of genetic or of environmental origin.4

These results further reinforce the need for exploring and treating rigorously risk factors in patients with a family history of death from CAD or CVD, since genetic factors should be considered as a risk factor by itself, like the other independent epidemiologic risk factors. In fact, a useful outcome of the knowledge of a family history of hypertension or CAD is to motivate the patients to follow their treatment for high blood pressure or risk factors more energetically.

THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Will gene markers help to identify patients predisposed to hypertension? There are no data on the number of genetic loci involved in the regulation of blood pressure, the frequency of deleterious alleles, the mode of transmission, or the quantitative effects of any single allele on blood pressure. The unimodal distribution of blood pressure within each age group and in each sex strongly suggests—but does not definitively prove—that several loci are involved. Because of the likely etiologic heterogeneity of the disease, it is difficult to expect that a single biochemical or DNA genetic marker will help the clinician in the management of most hypertensive patients. However, genetic markers are useful indicators for elucidating the various genetic loci linked to high blood pressure. The genetic approach can disregard a gene as being frequently and importantly implicated in the level of blood pressure or in hypertension. On the other hand, the discovery of a positive linkage between a given locus and high blood pressure will promote new studies for improving or finding new intermediate phenotypes of the locus. Molecular genetics can even unravel an underestimated or totally unexpected mechanism of blood pressure control.

Several biochemical markers linked to high blood pressure have been identified in the past. Such markers can be used to get close to a locus implicated directly or indirectly in blood pressure regulation. The most extensively studied phenotype marker is the Na+-Li+ countertransport, which is genetically inherited and under the control of a dominant gene but which has a small effect on blood pressure. 10 Another common phenotypic marker is the histocompatibility complex antigen (HLA) system, which was shown in 1 study to cosegregate in families affected with high blood pressure.11 High levels of urinary kallikrein excretion are under the control of a dominant gene and seem to be associated with a decreased risk of essential hypertension¹²: both adults and children with high urinary kallikrein excretion have less than half the rate of parental hypertension as individuals who had a low kallikrein genotype. At the present time, these phenotypic markers cannot be used to predict the risk for hypertension in a given subject. However, they are helpful indicators of the genetic loci that may be involved in blood pressure regulation.

DNA MARKERS: THE CASE OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM Glucocorticoid remediable aldosteronism:

AN EXAMPLE OF AN AUTOSOMAL DOMINANT DIS-EASE DUE TO A MUTATION OF A GENE OF THE RENIN-ALDOSTERONE SYSTEM: The mitochondrial enzymes belonging to the cytochrome P450 family are involved in adrenal steroid synthesis. They are not usually classified as enzymes of the reninangiotensin system, but aldosterone synthase is a key enzyme in the renin-angiotensin-aldosterone cascade, since it converts corticosterone into aldosterone. A particular form of hypertension due to a mutation of this enzyme has been recently identified. Glucocorticoid remediable aldosteronism, also called dexamethasone-suppressible aldosteronism, is rare autosomal dominant disease characterized by hypertension, a slight hypokalemia, a suppressed plasma renin activity, and a variable degree of aldosteronism. There is an abnormal urinary excretion of cortisol metabolites, 18oxocortisol, and 18-hydroxycortisol. All these abnormalities, including hypertension, can be corrected by suppression of adrenocorticotropic hormone (ACTH) by dexamethasone. It had been proposed that the disease was due to an abnormal expression in the zona fasciculata of aldosterone synthase. Recently, Lifton et al¹³ showed that this disorder was indeed due to an abnormal aldosterone synthase gene product present in the fasciculata zone of the adrenal gland. They studied a large kindred affected with this disease and found a gene duplication arising from unequal crossing over, resulting in a fusion of 11β-hydroxylase promotor with the coding sequence of aldosterone synthase. The chimeric gene encodes a protein that can hydroxylate cortisol (the steroid substrate present in the zona fasciculata) in the 18 position and that is under the control of 11B-hydroxylase, whose expression can be down-regulated by exogenous glucocorticoid administration. All the phenotypic abnormalities of glucocorticoid remediable aldosteronism can be explained by this mutation, which is the first known to be responsible for a monogenic disease of the renin-aldosterone system.

Essential hypertension: In the case of essential hypertension, it is unlikely that such a specific mutation can be demonstrated to be responsible for this disease from the arguments developed above. However, even though the genetic loci controlling blood pressure are unknown, a first and logical approach is to study genes that may contribute to the variance of blood pressure. The genes of the renin-angiotensin system are a good example of such an approach, since this system is well known to be involved in the control of blood pressure. The human renin gene is important because the renin-angiotensinogen reaction is the first, and rate-limiting, step leading to angiotensin II production. About 30% of subjects with essential hypertension have higher renin levels than do normotensive subjects of the same age when examined under the same metabolic conditions. 14 The amount of angiotensin I generated by renin depends not only on renin, but also on angiotensinogen, since the plasma angiotensinogen concentration is also rate limiting. It has been reported that angiotensinogen concentrations differ between normotensive and hypertensive subjects. 15

Finally, a subset of patients with essential hypertension have an abnormal response to angiotensin II. Angiotensin II infusion reveals that these subjects (nonmodulators) have a blunted response of aldosterone secretion or renal plasma flow, respectively, 16-19 when compared with normotensive and other hypertensive patients (modulators). This defect seems to be genetically inherited, appears to cosegregate with hypertension, and may be due to a genetic defect in the angiotensin II receptor or in the postreceptor signaling pathway. These phenotypes are of interest for the classification of hypertensive patients but may be secondary to high blood pressure rather than causally implicated in the disease. Genetic studies can solve this problem by establishing whether polymorphism of the genes is associated with, or linked to, high blood pressure (Figure 1).

The renin gene: The renin gene is likely to be one of the genes related to blood pressure in a rat model of genetic hypertension, the Dahl saltsensitive hypertensive rat. Polymorphism of the renin gene has been identified by Rapp et al²⁰ in both inbred salt-sensitive (S) and salt-resistant (R) hypertensive rats. These investigators searched for a cosegregation of renin alleles with blood pressure in rats obtained from crosses of S and R. Inbred S and inbred R strains were crossed to produce F1

rats, then a F1 × F1 cross was made to obtain a F2 generation. Blood pressure was measured in the F2 generation under a high salt diet, and the renin genotypes were determined. Blood pressure differed markedly among the renin genotypes in the F2 population. The rats with 2 renin homozygous genotypes (Ren^{RR} and Ren^{SS}) exhibited a mean 20 mm Hg blood pressure increase, and 1 S renin allele was associated with an approximate increase of 10 mm Hg in blood pressure. From this experiment, it was concluded that there was a clear cosegregation of the renin gene with elevated blood pressure and that this was likely to be one the few genes causally related to hypertension in Dahl salt-sensitive rats.

These results, although restricted to this particular strain of genetic hypertensive rat, prompted us to perform a prospective study in human subjects in which we compared the frequency of renin gene polymorphisms in normotensive and hypertensive white human subjects, with similar age, sex distribution, and body mass index.²¹ The familial susceptibility was defined as at least 1 parent and 1 sibling who were hypertensive before age 65 years, whereas the normotensive group had no familial history of hypertension. Renin gene polymorphisms located throughout the renin gene were identified using 3 restriction enzymes. There was no difference in allele or in haplotype frequencies between the

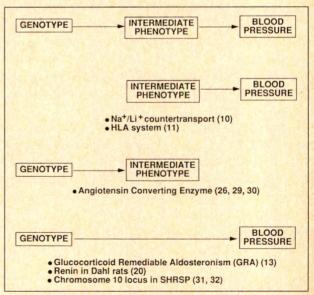


FIGURE 1. Relation between genotype, intermediate phenotype, and blood pressure level (distal phenotype). In rat or human essential hypertension, there has been no report of a direct chain between a gene variant, its effect on an intermediate phenotype, and its ultimate link with blood pressure level or hypertension. However, there have been discrete interactions along this chain of events, some of which are indicated in this figure. Numbers in parentheses refer to the literature quoted in the text.

hypertensive and the normotensive groups. No association was found between renin gene polymorphisms and essential hypertension.

This study, as well as the negative results from another population study²² and from a report on a large Utah pedigree with high prevalence of hypertension,²³ cannot definitively eliminate the implication of the renin gene in human hypertension, because of (1) the relatively low specificity of the renin markers used and (2) the lack of statistical power when reasonably sized population studies are performed. More statistical power can be achieved when linkage studies are performed in families or in sib pairs. Therefore, another study was conducted to test the hypothesis of a linkage between the renin gene polymorphism and hypertension, using the affected sib-pair method.²⁴ Sibpair analysis is an interesting alternative to large multigenerational pedigree studies for testing a linkage in a complex multifactorial disease. It has the advantage of not assuming any specific mode of inheritance and looking only for a distortion of segregation between a genetic marker and the disease. The renin genotype of the affected sib pairs was determined, and the allelic concordance between the sib pairs compared with the allelic frequency of the unrelated hypertensive population described above.²¹ This study did not show any excess of renin allele shared among the hypertensive sib pairs and therefore suggests again that the renin gene does not have a frequent or important role in the pathogenesis of human essential hypertension. However, it is not possible to exclude a minor role of this gene in blood pressure levels in a large population of patients, or a major gene effect in rare families.

The ACE gene: Angiotensin-I converting enzyme (ACE) is a zinc metallopeptidase whose main function is to convert angiotensin I into angiotensin II and to inactivate bradykinin. It has been assumed that this step of the renin-angiotensin system is not limiting, and indeed there is no indication that plasma ACE levels are related to blood pressure levels. Plasma ACE levels are remarkably stable when measured repeatedly in a normal subject but vary considerably (1-5-fold) between patients.²⁵ ACE variance cannot be explained by several hormonal and environmental factors and, therefore, is assumed to be under genetic control. This was shown by a study of plasma ACE levels conducted in normal nuclear families, which demonstrated the presence of a familial aggregation of ACE values and suggested a major gene effect, responsible for about 40% of total ACE variance.26

Cloning of human ACE cDNA²⁷ and of the ACE gene²⁸ allowed us to identify an insertion/ deletion polymorphism at the ACE gene locus.²⁹ This polymorphism consists of the presence or absence of a 250 base pair (bp) DNA fragment located within intron 16 of the ACE gene. Homozygous patients are classified as either II (I for insertion), or DD (D for deletion), a heterozygous patient being I/D.²⁹ A recent study in normotensive nuclear families combining cosegregation and linkage analysis showed that the variant I/D was not due to the insertion itself but was located within the ACE gene and therefore that the ACE gene controls plasma ACE levels.³⁰

ACE serum concentration is directly related to ACE genotype, as defined by the I/D polymorphism. In a study of 80 healthy subjects, mean serum ACE levels were 299, 392, and 494 µg/liter for II, I/D, and DD patients, respectively. In this study, the I/D polymorphism accounted for 47% of the total phenotype variance of serum ACE. The observation of a genetic polymorphism explains much of the interindividual variability of circulating ACE and has a direct clinical application. By simultaneously determining ACE genotype and plasma ACE levels, it is then possible to compare the ACE level of a given subject with the reference interval of normal patients carrying the same genotype. This has clinical implications in diseases such as sarcoidosis, where plasma ACE is a good indicator of the activity of the disease and of the effectiveness of the treatment.

The observation that plasma ACE levels are under direct control of variants of the ACE gene renders attractive the hypothesis of considering ACE as a possible candidate gene for high blood pressure, even though no relation was found between plasma ACE levels, ACE genotype, and blood pressure in our study on 98 nuclear families.³⁰ The blood pressure response to ACE inhibitors may also vary according to the I/D polymorphism of the gene, but this hypothesis has not yet been tested. Two recent studies performed in genetically hypertensive rats made this hypothesis even more attractive. 31,32 A F2 population from stroke-prone spontaneously hypertensive rats and normotensive Wistar Kyoto crosses was studied by 2 laboratories, using a set of markers evenly spaced throughout the rat genome. Contrary to the previously described strategy of the "candidate gene" approach, this strategy does not make any hypothesis as to a candidate gene but utilizes a collection of

polymorphic DNA markers and looks for their inheritance in a cross between 2 inbred parental strains. Both groups of investigators found a significant linkage between NaCl-loaded hypertension and a gene locus on chromosome 10. This locus contributed as much as 20% of blood pressure variance. Comparison of the human and rat chromosomal maps showed that the segment of rat chromosome 10 is conserved as a linkage group in human chromosome 17q, where ACE had been previously located.33 Rat ACE was found to be located on rat chromosome 10 without recombination with the growth hormone locus previously identified as linked to blood pressure values. The ACE locus was, therefore, significantly linked to blood pressure measurements and was a candidate gene for genetic hypertension.

The finding that ACE was one of the numerous genes linked to blood pressure variance in rat genetic hypertension prompted studies to detect possible linkage or association of this locus in human hypertension. In a recent study by Jeunemaitre et al³⁴ performed in hypertensive sib pairs from Utah with the use of a highly polymorphic marker, there was no evidence of any linkage between blood pressure levels and the ACE locus. Another study was performed by Harrap et al,35 who investigated the distribution of the I/D ACE gene polymorphism described above in young adults with contrasting genetic predisposition to high blood pressure. Young adults with high blood pressure and 2 parents with high blood pressure did not show any significant difference in the I/D allele frequencies of the ACE gene when compared with adults of the same age but with low blood pressure and no genetic predisposition to high blood pressure. Taken together, these results suggest that the ACE gene does not play a major role on blood pressure variance in these populations. However, it must be remembered that hypertensive patients were not challenged by a high salt regimen, whereas the blood pressure variance attributable to chromosome 10 locus in the rat was markedly influenced by dietary salt status. A more likely hypothesis is that other, yet unidentified, gene(s) on rat chromosome 10 (or putatively on chromosome 17q in humans) could be involved in high blood pressure levels. A more precise location of the predisposing gene in stroke-prone spontaneously hypertensive rats will be of great interest for future research in human hypertension. If the ACE gene is not linked to hypertension, it is interesting to note that the ACE I/D polymorphism seems to be a potent risk factor for coronary heart disease in

patients formerly considered at low risk according to common criteria.³⁶

The angiotensinogen gene: Plasma angiotensinogen concentration is a rate-limiting step in the renin-angiotensinogen reaction, at least under certain conditions such as in patients with high levels of renin or low levels of angiotensinogen. Angiotensinogen is expressed mainly in the liver but also in various tissues, where it can be locally cleaved to produce angiotensin I. Finally, there has been an indication that plasma angiotensinogen levels are higher in hypertensive than in normotensive subjects. 15 Therefore, angiotensinogen may be considered as a candidate gene for high blood pressure. Genetic studies on this gene have been hampered by lack of a DNA marker, since no restriction fragment length polymorphism has been identified. Recently, Kotelevstev et al³⁷ have described a very informative dinucleotide repeat sequence at the human angiotensinogen gene, which now allows performance of genetic studies in normotensive and hypertensive families. Recent studies of two large groups of hypertensive sibships showed evidence of genetic linkage between the angiotensinogen gene and hypertension, and demonstrated association of angiotensinogen molecular variants with the disease. Therefore, it is likely that molecular variants of angiotensinogen constitute inherited predisposition to hypertension.³⁸

CONCLUSION

Both epidemiologic and genetic studies indicate that a strong family history of hypertension and/or CVD is an independent risk factor for CVD. Management of the hypertensive subject should take into consideration the genetic factors as well as the classic epidemiologic risk factors. Patients with a strong family history of hypertension and/or of CVD should be carefully monitored for blood pressure levels and cardiovascular risk factors. If they are borderline hypertensive, they should be treated, at least by nondrug intervention, especially if they are young adults in whom high blood pressure may be of genetic origin. Both biochemical and now DNA markers are currently being evaluated regarding their contribution to blood pressure levels. At this time, it is likely that neither the renin nor the ACE genes contribute to a large extent to genetic hypertension, at least in humans. However, they could be still involved in a subset of the human population that has yet to be defined. Other genes of the renin-angiotensin-aldosterone system may play a role in genetic hypertension and are presently being investigated.

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Prevention of Myocardial Infarction

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Despite substantial progress in cardiovascular disease prevention, stroke and myocardial infarction remain the leading causes of death throughout the industrialized world. Treatment of high blood pressure, while contributing importantly to this progress, remains inefficient and less than optimally effective, particularly in regard to coronary artery disease events. Therapeutic intervention in the renin-angiotensin system offers promise of progress on both these fronts. Renin-sodium profiles have been shown to permit prognostic stratification of otherwise indistinguishable hypertensive patients. Indeed, low renin subjects, without other cardiovascular risk factors, have a particularly favorable prognosis. Now, the pharmacologic ability to mute the pathologic effects of angiotensin II also offers the genuine possibility that the cardioprotective value of antihypertensive therapy may be significantly improved.

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There have been spectacular reductions in the incidence of cardiovascular diseases in the past quarter century. In the United States, interventions based on the risk factor hypothesis have been largely responsible for a 57% decrease in the incidence stroke and a 47% decline in heart attack mortality. 1 Nevertheless, stroke and heart attack account for 40-50% of all deaths in developed countries and remain the leading causes of death.

EFFICIENCY OF ANTIHYPERTENSIVE CARE

Current antihypertensive management strategies result in treatment of many patients who are at vanishingly small risk of cardiovascular disease. This reflects the tremendous prognostic heterogeneity that characterizes patients classified primarily by level of blood pressure.2 It is possible, however, by assessment of risk factors and identification of preclinical end organ disease, as defined in the long-term Framingham study,² to stratify patients at the same level of systemic blood pressure into subgroups with vastly different expectations of subsequent disease events. Despite this capability, current antihypertensive treatment strategies largely ignore these clinical subtleties and generally apply interventions based on blood pressure levels alone. The result is that very many patients are treated, with measurable benefit being received by only a minority.

EFFICACY OF ANTIHYPERTENSIVE CARE

MacMahon et al³ and Collins et al,⁴ in an elegant analysis of the published observational studies of the natural history of hypertension and of the published clinical trials of antihypertensive therapy, have provided a means both to predict the potential results of treatment and to assess the actual benefit achieved. By combining several large population-based studies and correcting for inaccuracies introduced by variation in blood pressure measures, they were able to describe a linear relation between the magnitude of the blood pressure elevation and the likelihood of subsequent cardiovascular events. Meta-analysis of 14 unconfounded clinical trials also provided remarkably

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consistent results. Specifically, in observational studies, a 7.5 mm Hg increase in diastolic blood pressure was related to a 40% increase in incidence of stroke and a 28% increase in heart attacks. In actual clinical trials, a 5-6 mm Hg decrease in diastolic pressure was associated with about a 40% decline in stroke events, but only about a 14% decline in heart attacks. This 50% deficit between the observed and expected decrease in heart attacks cannot readily be explained by existing knowledge.

Several possible causes have been identified to explain the disappointing results in regard to coronary events. Diuretics have been used in all the clinical trials. Because they adversely affect lipid and glucose metabolism and electrolyte levels, it has been hypothesized that these alterations have muted the benefit of a lower blood pressure. 5 Beta blockers, which were used extensively in older trials, also distort lipid and glucose metabolism.6

In addition to the effects of a particular kind of drug, treatment itself has been implicated as carrying the potential for harm. It has been found, in a series of retrospective analyses of clinical trials as well as through examination of cohort studies, 7,8 that an increased incidence of myocardial infarction (MI) occurs in those patients whose blood pressure response to therapy was greatest or whose diastolic pressures fell to < 80 mm Hg.^{7,8} Although considerable controversy continues to surround this repeatedly demonstrated "J-shaped" phenomenon, it seems prudent to moderate blood pressure reduction, particularly among patients with evidence of preexisting coronary artery disease.

The great challenge to modern antihypertensive practice, then, is to improve both the efficacy and efficiency of antihypertensive care. Treatment needs to reach those most likely to have heart attacks and

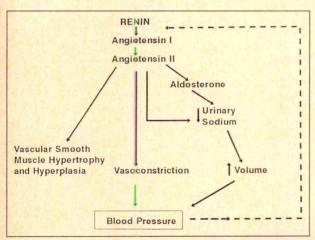


FIGURE 1. Vasoconstriction-volume hypothesis and the renin axis.

strokes and to be more successful in reducing the heart attack rate of those who are treated.

THE RENIN-ANGIOTENSIN SYSTEM AND **CORONARY ARTERY DISEASE**

A fruitful avenue of inquiry, based on investigation of human blood pressure control mechanisms, has shown that malfunction of the renin-angiotensin system may help to explain both the clinical heterogeneity of hypertensive patients and the apparent failure of current antihypertensive treatment to realize its full potential. Over the past half century, the sodium-renin-angiotensin-aldosterone axis has proved to be a powerful instrument for the analysis of blood pressure control. Analysis of this system has also provided a framework for the selection of antihypertensive therapy. This servocontrol feedback mechanism integrates plasma volume and vasoconstriction in the expression of systemic blood pressure. Renin stimulates the conversion of angiotensinogen to angiotensin II (Figure 1), which is the most powerful vasoconstrictive agent known. Renin also contributes to volume expansion, indirectly by stimulating aldosterone secretion and directly by increasing renal tubular sodium resorption. An increasing arterial pressure then provides the signal to suppress renin secretion. These specific biochemical actions have provided convenient sites to guide pharmacologic interventions that can lower pressure by altering physiology.

More recently, however, it has become clear that the renin-angiotensin system, particularly through expression of angiotensin II, can also produce vascular damage. In both experimental animals¹⁰ and in human investigations,¹¹ it has been possible to demonstrate that angiotensin II stimulates vascular smooth muscle mitogenesis and cellular hypertrophy. The net result of these effects on the vascular wall can be to impede blood flow and produce hypoxic target organ damage.

Some 20 years ago, Brunner et al12 postulated the clinical relevance of these physiologic relationships. In a retrospective analysis of 240 hypertensive subjects, they found that the sodium-to-renin relation provided a convenient means to stratify patients into subgroups with different levels of cardiovascular risk. A prospective study has now confirmed this hypothesis. 13 Plasma renin activity and urinary sodium excretion of 1,717 mild and moderately hypertensive subjects were determined before the initiation of antihypertensive therapy. Over a follow-up period of 8 years, blood pressure control was maintained by application of a modified stepped-care regimen by therapists blinded to the renin profile status. Some 58 cardiovascular morbid and mortal events were observed during follow-up, including 27 MIs and 12 strokes.

The renin/sodium profile was used to stratify patients into high (12%), normal (56%), and low (32%) renin status. In this study, younger white men were most likely to have high, and older black women were most likely to have low, renin levels. Some minor pretreatment differences in blood pressure existed between groups, but throughout follow-up, blood pressure control was good and equivalent in the 3 groups. No differences were found in prior cardiovascular disease, lipid or glucose metabolism, or left ventricular hypertrophy (LVH) between groups. Drug use was similar in the 3 groups, with diuretic use, initially most common, increasingly replaced by calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and α blockers. Throughout, β blockers were used by about 25% of patients.

The principal finding of the study was that patients with a high sodium/renin profile were at greatest risk of MI (Table I). Multivariate analysis confirmed the significance of an elevated renin profile as an independent predictor of MI. In fact, among these patients, in addition to renin profile status, only cholesterol, LVH, gender, and cigarette smoking were independently associated with the risk of MI. No measure of blood pressure in these successfully treated hypertensive patients remained in the multivariate analysis model as predictive of MI.

Bivariate analysis revealed that, in general, the renin profile-to-MI relation persisted regardless of gender, age, the presence or absence of hypercholesterolemia, smoking, or fasting blood sugar level (Figures 2 and 3). However, in certain situations, that was not the case. In particular, the renin profile-to-MI relation, most dramatically displayed in whites, did not appear among blacks. However, since MI was relatively rare in blacks treated in this study, the paucity of events affected the statistical power to test this relation. 14 It should also be noted that the renin/sodium profile was not associated with stroke, although, again, the number of such events was small. Finally, when patients were stratified according to the presence or absence of other risk factors (Figure 4), the renin profile remained a powerful discriminator of risk.

An earlier retrospective analysis of 1,999 persons drawn from a general population indicated that no relation existed between plasma renin and cardiovascular disease. 15 Many important method-

TABLE I Unadjusted and Adjusted Incidence of Myocardial Infarction Per 1,000 Person-Years, According to Renin Profile*

	Renin Profile			
Variable	High	Normal	Low	Rate Ratio†
No. events	7	15	5	
Follow-up (person- years)	539.3	2,851.8	1,519.8	-
Unadjusted incidence	13.0	5.3	3.3	3.9 (1.2-12.3)
Adjusted incidence	14.7	5.6	2.8	5.3 (3.4-8.3)

*The incidence was adjusted for distributional differences in age, sex, and race with the entire study population used as the standard.

†The rate ratio is that between the high-profile and low-profile groups. Values in parentheses are 95% confidence intervals.

ologic differences between that earlier study and the current prospective study make comparison difficult. Nevertheless, in that report >95% of patients were normotensive. The possibility certainly exists that plasma renin and the renin profile may have prognostic value primarily in hypertensive patients. In other words, variations in plasma renin among normotensive patients may reflect appropriate physiologic response to maintain blood pressure and flow. In contrast, among hypertensive patients, where renin levels would be expected to be set at or near 0, any substantial elevation can be pathologic. 16 In this regard, it is of note that when our patients were stratified by level of diastolic pressure, elevated renin levels were most predictive of hypertensive events among those with the highest pressures. In fact, among patients with diastolic pressures < 95 mm Hg, high renin subjects were not at significantly greater risk than normal or low renin subjects. This, at first glance, would suggest that the 2 studies may be compatible. However, the small number of events observed among the hypertensive patients (n = 6) with pressures < 95 mm Hg precludes drawing a definitive conclusion.

Of particular note is the finding that in patients with no other risk factors who also had a low renin/sodium profile, not a single MI infarction occurred over 8 years of follow-up. Overall, 240 subjects, or 14% of the total, fell into this seemingly protected subgroup.

Because of the strong inverse relation of sodium ingestion and plasma renin levels (Figure 5), the renin profile was designed to take sodium intake into account. In an attempt to determine whether sodium intake might have an additional, independent impact on the occurrence of MI, we determined the incidence of myocardial infarction in patients stratified both by the renin profile and by whether their sodium intake was above or below the median for the group (126 mmol/24 hours). The analysis was limited to men, in whom 82% of

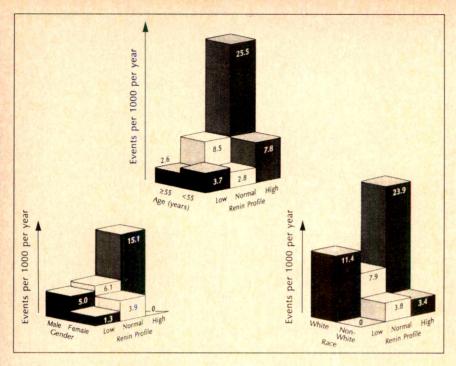


FIGURE 2. Myocardial infarction incidence by renin profile and age, gender, and race.

MIs occurred. It can be seen that in both sodium intake strata, the renin profile is a powerful predictor of subsequent events (Figure 6). In addition, within each renin profile category (high, normal, and low), those consuming a lower sodium diet were at greater risk of subsequent events. This occurred despite the fact that there were no significant differences among the 6 subgroups in age, race, presence of LVH, cigarette smoking, or pre- or in-treatment blood pressure. As expected,

stratification by sodium intake revealed that, for example, high renin subjects consuming less salt had a slightly higher absolute plasma renin activity (7.47 vs 5.24 ng/mL/hour) than those consuming more sodium. This analysis is ongoing, but the available data confirm the well-recognized relation between sodium intake and plasma renin activity and suggest that, at the very least, a low sodium intake, which elevates plasma renin, may not be beneficial for treated hypertensive patients.

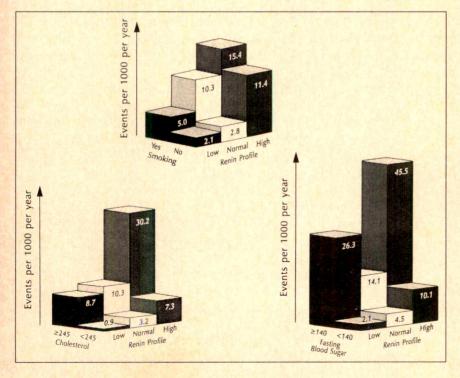


FIGURE 3. Myocardial infarction incidence by renin profile and cholesterol, fasting blood sugar, and smoking.

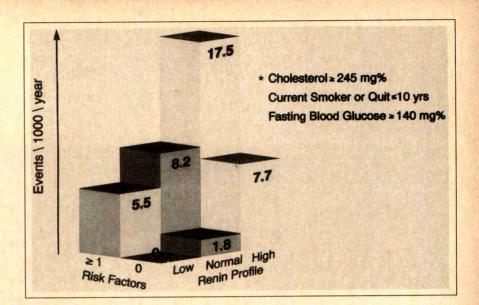


FIGURE 4. Myocardial infarction incidence by risk factor status* and renin profile.

THE RENIN SYSTEM AND ANTIHYPERTENSIVE THERAPY

Clearly, appreciation of the renin-angiotensin system has now passed beyond merely being perceived as a participant in the mechanisms for blood pressure control. Instead, a more profound understanding of the full biologic significance of the renin-angiotensin system suggests that treatment regimens can be more rationally designed to improve both the efficiency and the efficacy of antihypertensive therapy. 16 First, the available data suggest that those hypertensive patients who have no evidence of preclinical end-organ disease, have a favorable risk factor profile, and are in the low renin profile category are at exceedingly low risk of subsequent cardiovascular disease events. Since these observations have been made in a cohort of successfully treated hypertensive patients, a prospective clinical trial is still needed to test the hypothesis that such patients may do as well with as without drug therapy. A positive finding in such an

experiment would make it possible for a sizable fraction (perhaps 15%) of mild-to-moderate individual hypertensive patients to avoid the cost, inconvenience, and possible harm of drug therapy, while producing substantial savings for society as a whole.

At the same time, elevated renin levels in the presence of elevated systemic blood pressure prospectively identifies that subgroup of hypertensive patients who can be expected to experience an increased incidence of MI, enabling them to receive special attention and, it is hoped, more appropriately tailored and effective therapy. The clinical data, combined with substantial animal and some human experimental evidence of end-organ damage associated with elevated angiotensin II levels, strongly support the view that the reninto-MI relation is causal. Although no clinical trial has tested the hypothesis that inhibition of the renin system with an ACE inhibitor would enhance the cardiovascular protection produced by tradi-

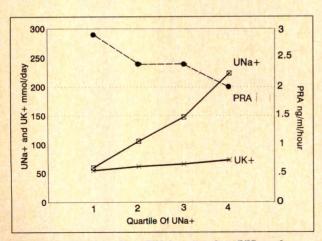


FIGURE 5. Urinary sodium (UNa), potassium (UK), and plasma renin (PRA) in untreated hypertensive men.

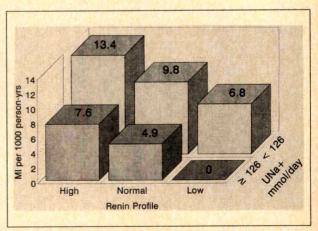


FIGURE 6. Renin profile, urinary sodium (UNa), and myocardial infarction (MI) among hypertensive men.

tional diuretic and B blocker therapy, available evidence offers encouragement. In particular, Dahlof et al¹⁷ have shown that vascular changes associated with hypertension are more completely reversed when patients are treated with converting enzyme inhibitors than with diuretics, despite the fact that blood pressure reduction was fairly similar in the 2 groups. These findings suggest the possibility that blood pressure control coupled with suppression of the renin-angiotensin system may close the gap between what is expected and what can be achieved by blood pressure reduction. Moreover, the existence of pharmacologic means to lower pressure by inhibiting angiotensin II generation offers the prospect that blood pressure reduction achieved in this way may yield cardiovascular protection even beyond that ascribable to the blood pressure change itself.

Finally, there is the possibility that normotensive patients with elevated renin levels may be at greater risk of cardiovascular events than their low renin confreres. Although no evidence exists to support this hypothesis, since more than half of all heart attacks occur among normotensive persons, the availability of a precise biologic marker to identify and perhaps suggest an effective intervention would be of enormous public health value.

CONCLUSION

Application of our knowledge of the reninangiotensin system is central to understanding and treating hypertensive disease. Available knowledge already makes it clear that the ability to quantitate the activity levels of the renin system accurately now provides the means to unravel the prognostic heterogeneity of hypertension and to describe blood pressure control mechanisms as the basis for rational therapeutic intervention. In addition, there is the possibility that manipulation of the reninangiotensin system may dramatically improve the capacity of antihypertensive therapy to prevent coronary artery disease in millions of hypertensive patients.

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Trandolapril in Hypertension: Overview of a New Angiotensin-Converting Enzyme Inhibitor

Laurent Nguyen Cong Duc, MD, and Hans R. Brunner, MD

Trandolapril is a new angiotensin-converting enzyme (ACE) inhibitor that has been extensively investigated in vitro, in animals, in normal volunteers, and in hypertensive patients. It has been shown to exert all the effects typical for the class of ACE inhibitors, and has a marked impact on the reversal of structural hypertrophy of the myocardium and the arterial wall. Trandolapril is a prodrug that must be hydrolyzed to its active metabolite, trandolaprilat. This latter compound exhibits a particularly high affinity for converting enzyme, which results in a slow dissociation and one of the longest durations of action of any converting enzyme inhibitor known so far. Trandolapril reduces blood pressure consistently throughout the 24-hour period following intake. Accordingly, trandolapril, more than any other drug of its class, can be considered a true, oncea-day antihypertensive drug.

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ngiotensin-converting enzyme (ACE) inhibitors provide an excellent approach to the treatment of patients with hypertension. ACE inhibitors have been available for clinical use for >15 years. They have been extensively studied and have been found to be both effective and well tolerated.

These agents share the common mode of action of ACE inhibition, which results in the blockade of the renin-angiotensin system (Figure 1). They interfere with the cleavage of angiotensin I to the active pressor agent angiotensin II, thus significantly decreasing circulating levels of the latter. Converting enzyme inhibitors also affect at least 2 other major natural hormonal systems: they prevent the breakdown of the vasodilator agent brady-kinin into inactive peptides and they modulate the production of prostaglandins.

Angiotensin II is a potent direct pressor agent on vascular smooth muscle and consequently ACE inhibition produces a direct peripheral vasodilation. Angiotensin II normally interacts with the autonomous nervous system. It enhances sympathetic nervous activity by potentiating the release and increasing reuptake of norepinephrine by the sympathetic nerve terminals. In addition, it tends to attenuate parasympathetic nervous activity. Inhibition of the renin-angiotensin system blunts the stimulating effects on the sympathetic nervous system and leads to further decrease in peripheral resistance. Angiotensin II stimulates the secretion of antidiuretic hormone and the release of the salt-retaining hormone aldosterone. ACE inhibition results in the decrease of circulating plasma aldosterone levels and reduces sodium and water retention. Further, recent experimental evidence strongly suggests that angiotensin II may exert a major influence by acting as a growth factor.

Compared with other antihypertensive agents, ACE inhibitors possess a very favorable hemodynamic profile. They lower blood pressure by reducing total peripheral vascular resistance very effectively, without influencing cardiovascular reflexes. Inhibition of the activation of the sympathetic

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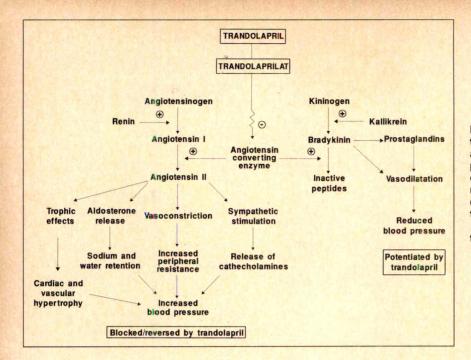


FIGURE 1. Simplified representation of the renin—anglotensin—aldosterone and kallikrein—kinin—prostaglandin systems, their effects on cardiovascular homeostasis, and the consequences of trandolapril administration. + indicates activation; — indicates inhibition. (Modified from Drugs.¹)

nervous system prevents the occurrence of any reflex acceleration of heart rate and thereby avoids any increase in myocardial oxygen consumption. Cardiac output and stroke volume remain nearly unchanged in patients with mild-to-moderate hypertension treated with ACE inhibitors and tend to increase toward normal levels in patients with left ventricular dysfunction, mainly as a consequence of reduced afterload. Regional renal, cerebral, and coronary blood flow are maintained, and local autoregulatory mechanisms are respected. Treatment with ACE inhibitors does not alter the blood lipids or the glucose balance.

In this context one of the most recent additions, trandolapril, is of particular interest. The purpose of this article is to provide a short review of some of its main characteristics.

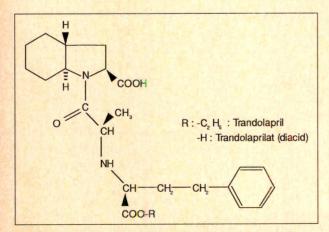


FIGURE 2. Chemical structure of trandolapril and trandolaprilat.

PHYSICOCHEMICAL AND PHARMACODYNAMIC PROPERTIES

Chemical structure: Trandolapril is the international nonproprietary name for [2S-(1(R'(R')), 2α , $3a\alpha$, $7a\beta$)]-1-[2-[(1-(ethoxy-carbonyl)-3-phenyl-propyl)amino]-1-oxopropyl] octahydro-1H-indole-2-carboxylic acid (Figure 2), a new orally active nonsulfhydryl ACE inhibitor. Since the active moiety of trandolapril is the free acid resulting from an ester cleavage, trandolapril is considered to be a prodrug, but one study has suggested that the hydrolysis into the diacid form is not a mandatory step for achieving ACE inhibition either in vitro or in vivo.²

Lipophilicity: The lipophilicity of trandolapril and trandolaprilat was studied by the reversed phase high-performance liquid chromatography method and compared to that of other ACE inhibitors.³ The lipophilic indexes, calculated at pH 7.4, are shown in Table I. The lipophilicity of trandolapril is intermediate between that of ramipril and perindopril, with captopril being more hydrophilic than the other compounds, whereas trandolaprilat is the most lipophilic diacid of the series studied. This high lipophilicity may contribute to a good penetration into various tissues, especially the heart muscle and the vascular walls, and accordingly to the marked inhibition of local converting enzyme.

ACE inhibition: Preclinical in vitro and in vivo studies have shown that trandolapril is a very potent and long-acting ACE inhibitor.

In vitro, trandolapril is more potent than enala-

pril (i.e., smaller concentrations are needed to inhibit 50% of ACE [IC₅₀]) whatever the origin of serum ACE tested (Table II).⁴ Trandolapril itself may exert direct ACE inhibition, since the IC₅₀ of unchanged trandolapril for human ACE is only 7-fold higher than that of trandolaprilat.

The inhibition of angiotensin I-induced pressor responses and the potentiation of bradykinin-induced depressor responses are good indicators of the effect of ACE inhibitors in vivo. After oral or intravenous administration to rats and/or dogs trandolapril attenuated the pressor action of angiotensin I and potentiated the depressor action of bradykinin.⁵ Trandolapril was 2.3- to 10-fold more potent than enalapril in all experiments, depending on species or route of administration.

In addition to the uptake into tissue sites from circulating plasma, recent data demonstrated that angiotensin II is locally generated in many organ tissues involved in cardiovascular regulation. Inhibition of ACE activity in tissues with subsequent local reduction of angiotensin II levels could significantly contribute to the antihypertensive effects of ACE inhibitors. Following a single oral administration in rats, trandolapril (3-100 µg/kg) and enalapril (10-300 µg/kg) inhibited ACE activity in serum and various tissues⁶ (Table III). Inhibition was maximal at 2 hours, and with trandolapril it was maintained for 24 hours. Trandolapril was 6to 10-fold more potent than enalapril except in the heart and adrenal glands, where the difference was higher.

In humans onset of ACE inhibition is very rapid—within 30 minutes after single oral dosing in healthy volunteers. Maximum inhibition is observed from 2–4 hours onward and marked ACE inhibition is observed for up to 24 hours. At doses of 2 mg, 80% of ACE activity is still inhibited 24 hours after administration of trandolapril. Similar patterns of ACE inhibition have been seen in elderly and younger hypertensive patients and patients with chronic renal impairment after repeated administration.

The effects of various doses of trandolapril on ACE activity were studied in humans. Trandolapril was administered to normal volunteers at daily doses of 0.5, 2, or 8 mg for 10 days. ACE activity was measured in vitro using 3 different synthetic substrates. Although the degree of ACE inhibition assessed with the 3 methods varied widely, all methods clearly indicated dose-dependent ACE inhibition that was paralleled by a dose-dependent increase in plasma active renin and blood angiotensin I levels. ¹⁰ This did not result in a dose-

TABLE I Lipophilic Index of Trandolaprill and Trandolaprilat Compared With That of Other Angiotensin-Converting Enzyme (ACE) Inhibitors

ACE Inhibitors	Lipophilic Index* (logkw ^{7.4})
Ramipril	2.34 ± 0.06
Trandolapril	1.49 ± 0.11
Perindopril	0.94 ± 0.06
Captopril	0.08 ± 0.03
Diacid Metabolites	
Trandolaprilat	1.46 ± 0.12
Ramiprilat	0.92 ± 0.08
Perindoprilat	0.87 ± 0.03
Enalaprilat	0.11 ± 0.03
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*The lipophilic index is expressed as the capacity factor (logkw^{7,4}) determined by reversed phase high performance liquid chromatography method.

TABLE II Angiotensin-Converting Enzyme Inhibitory Activity of Trandolapril, Enalapril, and Their Diacids In Vitro

	IC ₅₀		
	Rat	Dog	Human
Trandolapril	1.7 ± 0.7	368 ± 50	7.1 ± 2.1
Trandolaprilat	1.6 ± 0.7	2.5 ± 0.1	0.9 ± 0.3
Enalapril	7.5 ± 2.9	$1,020 \pm 200$	593 ± 208
Enalaprilat	4.7 ± 0.9	7.8 ± 2.2	2.9 ± 1.4
IC ₅₀ : concentration of	of drug (nM) needed	to inhibit 50% of seru	m ACE.

TABLE III Angiotensin-Converting Enzyme (ACE) Inhibition in Serum and Tissues Following a Single Oral Administration of Trandolapril and Enalapril in Rats

	ID ₅₀	
	Trandolapril	Enalapril
Serum	4.0 ± 0.5	47.5 ± 6.3
Heart ventricle	20.5 ± 3.5	>300*
Aorta	19.7 ± 2.8	137.8 ± 33.8
Lung	7.7 ± 0.9	53.1 ± 8.4
Kidney	6.7 ± 0.8	57.8 ± 9.3
Adrenal medulla	10.8 ± 0.9	>300*
Adrenal cortex	21.0 ± 2.1	>300*

*Enalapril produced a plateau inhibitory effect of 40% only.

ID₅₀ = dose (µg/kg) ± SEM producing 50% of the maximum ACE inhibition.

dependent decrease in plasma angiotensin II levels, presumably because of the induced increase in renin and angiotensin I, which was still partially converted to angiotensin II. These results showed that it is not worth increasing the doses of an ACE inhibitor unnecessarily and doses ranging from 0.5–2 mg trandolapril achieved effective ACE inhibition without any major stimulation of the reninangiotensin system.

PHARMACOKINETIC PROPERTIES IN HUMANS

Oral trandolapril is rapidly absorbed from the gastrointestinal tract and within 1 hour reaches peak plasma concentrations in a dose-dependent fashion. The plasma half-life of trandolapril is 0.7 hour. Approximately 40–60% of an administered

dose is absorbed¹² and this percentage is unaffected by food.13

After absorption, trandolapril is hydrolyzed to the active diacid metabolite trandolaprilat. Trandolaprilat reaches peak plasma concentrations at 6 hours. With once-daily dosing, steady state is reached within 4 days in healthy subjects,9 elderly or younger hypertensive patients,8 and in patients with chronic renal failure.9 As is the case with several other ACE inhibitors, trandolaprilat has a polyphasic elimination profile with a slow terminal phase, probably the result of binding to ACE and subsequently a slow dissociation from the enzyme. 14 The effective half-life for accumulation of trandolaprilat has been estimated to be in the range of 16-24 hours. Once administered, 80% of the circulating trandolapril and up to 94% of the circulating trandolaprilat are bound to plasma proteins. This protein binding is not saturable for trandolapril and is saturable for trandolaprilat.

After single oral dosing of 14C-labeled compound, elimination is rapid, 82% of the radioactivity is eliminated within 48 hours, and excretion is nearly complete after 7 days. Pharmacokinetic analysis revealed that urinary and fecal recoveries of radioactivity accounted for 33% and 67% of the total excretion, respectively. 15 Only negligible quantities of unchanged trandolapril are excreted in urine. The majority of renal excretion products is trandolaprilat and its glucuronide conjugate. Both trandolapril and trandolaprilat are also metabolized to inactive diketopiperazine derivatives to a limited extend.

In the presence of normal hepatic and renal function, age alone does not have any significant influence on trandolaprilat pharmacokinetics.

In patients with various degrees of renal impairment the renal clearance of trandolaprilat decreases with increasing renal insufficiency, leading to increased plasma concentrations. The pharmacokinetics of trandolaprilat are thus significantly altered when creatinine clearance decreases to < 30 mL·min⁻¹/1.73m². Thus, trandolapril dosage adjustment (i.e., a low starting dose of 0.5 mg) is required in patients with severe renal impairment.

Interaction studies were performed with drugs commonly used in clinical practice. No significant changes in pharmacokinetics are observed when trandolapril is administered concomitantly with digoxin, 16 nifedipine, 17 and furosemide. 18 Trandolapril does not alter the anticoagulant properties of warfarin.19

EFFECTS OF ACE INHIBITION ON STRUCTURAL AND FUNCTIONAL CHANGES OF THE HEART AND THE ARTERIES SECONDARY TO **HYPERTENSION**

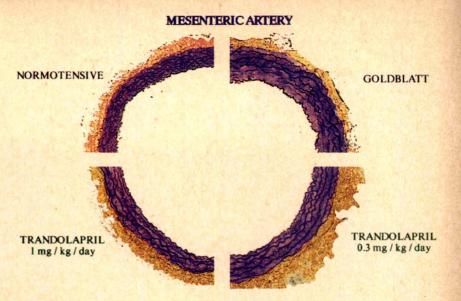
The structural changes observed in the heart and the arterial wall of hypertensive patients lead to deleterious cardiovascular complications. Bevond blood pressure reduction, the prevention of these changes is one of the most important clinical challenges. Thus, hypertension is associated with left ventricular hypertrophy, an independent risk factor, and changes in arterial wall structures and functions: hypertrophy of smooth muscle cells, increase in collagen matrix density, and reduction of arterial compliance, a common index for measuring the stiffening process.

The effects of trandolapril on these alterations were studied using a Goldblatt (2 kidneys, 1 clip) rat model of renovascular hypertension. After oral treatment at 0.3 and 1 mg/kg/day for 4 weeks, trandolapril induced a dose-dependent regression of cardiac hypertrophy, nearly complete at the higher dose: heart weight-to-body weight ratio decreased by 17% and 30% at 0.3 and 1 mg/kg/ day, respectively. A marked decrease in vascular wall hypertrophy in both the mesenteric artery and the aorta were also observed.²⁰ Again, complete normalization of media thickness was observed compared with the normotensive control group at 1 mg/kg/day (Figure 3).

In another study, trandolapril 0.4 mg/kg/day was given orally for 4 weeks to 20-week-old spontaneously hypertensive rats (SHR), a widely used model of genetic hypertension. In comparison with the control group, a decreased blood pressure (-15 to -18%), a regression of myocardial hypertrophy (-9%), reductions of media thickness of thoracic aorta (-11%) and femoral arteries (-12%), and an increased compliance of the resistance arteries were observed in the trandolapril-treated group.²¹

These effects were also observed in aged SHRs with congestive heart failure in which hypertension and cardiovascular changes had been established for a long time. Twenty-one-month old SHRs received placebo, trandolapril 0.3 mg/kg/day, or enalapril 10 mg/kg/day for 3 months.²² Despite a nonsignificant decrease in blood pressure, trandolapril induced a reversion of cardiac hypertrophy (i.e., 24% decrease of ventricular hypertrophy and a reduction of the septal thickness; Figure 4) and a regression of aortic wall hypertrophy. Enalapril produced similar effects on all these parameters, but only trandolapril induced a near complete

FIGURE 3. Cross-sections of a mesenteric artery of a normotensive control rat and Goldblatt (2 kidneys, 1 clip) rats treated with placebo, trandolapril 0.3 mg/kg/ day, or trandolapril 1 mg/kg/day for 4 weeks. A decrease in vascular wall hypertrophy is observed in the trandolapril-treated animals, and a complete normalization of media thickness is achieved with the 1 mg/kg/day dose.



regression of media hypertrophy of the mesenteric arteries with decreases in myocytes surface (-42%)and extracellular matrix (-22%), and an increase in nuclear density (68%) (Figure 5). Compared with the placebo group (58% mortality), the survival was greatly improved in both active treatment groups (20% mortality).

In 15 hypertensive patients De Luca et al²² reported that 1-year treatment with trandolapril 2 mg once daily induced a normalization of blood pressure (systolic and diastolic blood pressures \leq 140 and \leq 90 mm Hg, respectively), a complete reversal of left ventricular hypertrophy with unchanged left ventricular systolic function, and increased diastolic function evaluated by echocardiography, and an increase in brachial artery compliance.23 After 1 month washout period, the

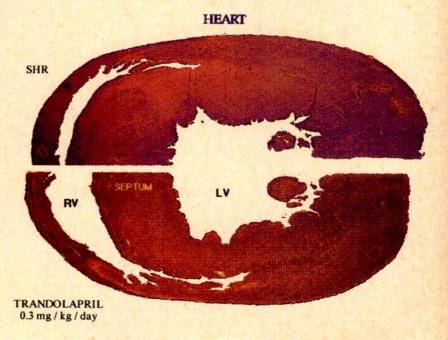
systolic and diastolic blood pressures returned to baseline values, whereas the left ventricular mass index and the brachial artery compliance remained different from baseline. Thus, long-term treatment with trandolapril is associated with a stable regression of cardiac and vascular abnormalities.

CLINICAL EFFECTS

The antihypertensive efficacy of trandolapril has been evaluated in 1,959 patients with various degrees of hypertension—67% mild, 30% moderate, and 3% severe.

Dose-ranging studies in double-blind, parallelgroup, placebo-controlled design were conducted. In one study of 186 hypertensive patients, comparing the placebo to 0.5, 1, and 2 mg trandolapril given once-a-day for 4 weeks, the lowest effective

FIGURE 4. Cross-sections of a heart of an aged spontaneously hypertensive rat (SHR) treated with placebo or trandolapril 0.3 mg/kg/day for 3 months. Trandolapril induced a decrease of ventricular hypertrophy with a reduction of septal thickness. LV = left ventricle; RV = right ventricle.



dose for diastolic and systolic blood pressure reductions were 1 and 0.5 mg, respectively²⁴ (Figure 6). At the end of the study, the 1 and 2 mg doses were equally effective, with a mean reduction of diastolic blood pressure of 13.9 and 12.3 mm Hg, respectively. The 2 mg dose, however, was effective more rapidly than the lower dose—within 7 versus 14 days. Moreover, this study showed a dose–effect relation between systolic blood pressure decreases and doses from 0.5–2 mg.

The efficacity of trandolapril at rather small doses was confirmed in another study in 216 hypertensive patients comparing placebo to 2, 4, and 8 mg trandolapril given once daily for 8 days. The 2 mg dose was effective in lowering the diastolic and systolic blood pressures. There was no difference between 2, 4, and 8 mg, suggesting that a plateau effect was obtained with the lowest dose used. This study demonstrated also that the ratio of the trough/peak effect was about 70% for the 3 trandolapril doses. This indicates that the blood pressure reduction is well maintained over the 24-hour period.

The long duration of action of trandolapril was confirmed with 24-hour ambulatory blood pressure (ABP) measurements. A double-blind parallel-group ABP monitoring study in 27 hypertensive patients comparing 1 and 2 mg doses given once daily for 14 days showed that the reductions in

blood pressure following intake were well maintained throughout the subsequent 24-hour period with no alteration of the circadian profile of blood pressure. Entry blood pressure remained decreased after the treatment was stopped and started progressively to return to initial levels within 48 hours after the last dose without any rebound effect.

Six large-scale comparative trials with the main classes of antihypertensive agents showed that 1-4 mg trandolapril monotherapy given once daily for 6-8 weeks reduced blood pressure in 59-77% of all patients with essential hypertension; the mean rate of responders was 64%. A responder patient was defined as having a supine diastolic blood pressure < 90 mm Hg or a diastolic blood pressure decrease of ≥10 mm Hg during treatment.²⁷ The average decline in diastolic blood pressure was 11-14 mm Hg, which is equivalent to that of reference drugs from the 4 major classes tested: ACE inhibitors (enalapril, captopril, and lisinopril), a β-blocking agent (atenolol), a diuretic (hydrochlorothiazide), and a calcium antagonist (nifedipine SR). In addition, concomitant administration of trandolapril and hydrochlorothiazide or nifedipine SR was generally more effective in lowering blood pressure than either monotherapy, as previously described in the literature with such combinations.

In long-term treatment the efficacy of trandola-







SH CONTROLS

TRANDOLAPRIL

ENALAPRIL

FIGURE 5. Electron micrographs of the muscular layer of a mesenteric artery. Aged spontaneously hypertensive (SH) rats were treated with placebo, trandolapril 0.3 mg/kg/day, or enalapril 10 mg/kg/day for 3 months. Trandolapril induced a marked reduction of myocyte surface and extracellular matrix. EL = elastic lamina; En = endothelium; L = lumen; Ma = interstitial matrix; My = myocyte; Nu = nucleus.

pril was well maintained. An interim analysis of a 14-month open study in 1,049 hypertensive patients treated with 2 or 4 mg trandolapril or a combination with a diuretic and/or a calcium antagonist showed a mean reduction of supine diastolic and systolic blood pressure of 13.3 and 18.5 mm Hg, respectively, with no evidence of loss of efficacy throughout the months. In comparison with the overall population, no major difference in efficacy was noted in 229 obese patients, 57 patients with glucose intolerance, or 60 patients with high serum creatinine at entry. Not surprisingly, a slightly greater decrease in systolic blood pressure (i.e., mean decline of 24 mm Hg) was obtained in 100 elderly patients whose systolic blood pressure was higher at baseline than that of the overall population.

The tolerance of trandolapril was evaluated in 1,959 patients treated for periods ranging from 1 week to 14 months, which represents 1,134 patient-years. Trandolapril was well tolerated at all doses used, 0.5–8 mg. The profile of adverse events of trandolapril was comparable with that of the other ACE inhibitors and better than that of the diuretic and the calcium antagonist used. In common with

other ACE inhibitors the most frequent adverse events associated with trandolapril in the long-term study were cough (3.9%), headache (2.3%), asthenia (2.1%), dizziness (1.7%), hypotension (0.5%), nausea (0.5%) and pruritus (0.5%). These adverse events led to discontinuation of the treatment in 7.2% of the patients. There was no evidence of drug-related hematologic or biochemical abnormalities. No significant changes in blood glucose, lipid, or electrolyte levels were observed.

CONCLUSION

ACE inhibitors are now well established as antihypertensive drugs. They have been demonstrated to be efficacious and to exhibit an extremely favorable therapeutic profile as to blood flow distribution, metabolic effects on electrolytes, glucose and lipid homeostasis, as well as interaction with the autonomic nervous system. Moreover, there is accumulating experimental and some preliminary clinical evidence suggesting that ACE inhibitors may exert some actions that go beyond simple blood pressure reduction, such as reversal of hypertension-induced left ventricular hypertrophy and thickening of the arterial wall.

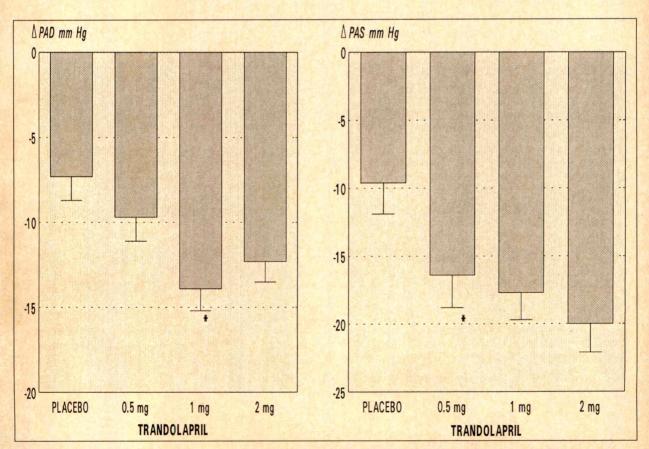


FIGURE 6. Mean decrease (\pm SEM) in supine diastolic and systolic blood pressure induced by 0.5, 1, and 2 mg trandolapril: a double-blind, parallel-group, placebo-controlled study; Δ PAD = decrease in diastolic blood pressure; Δ PAS = decrease in systolic blood pressure; *first effective dose significantly different from placebo (Williams test).

Trandolapril is a relatively recent addition to the class of ACE inhibitors. As a prodrug, it has to be hydrolyzed to the active drug trandolaprilat. This compound has been investigated extensively in experimental situations and in hypertensive patients. It has been shown to exhibit all the effects that are typical for all ACE inhibitors and has a marked impact on the reversal of structural hypertrophy of the myocardium and the arterial wall. In addition it is characterized by a high affinity to the converting enzyme and by one of the longest duration of action of any ACE inhibitor available

ABP monitoring in hypertensive patients demonstrated that trandolapril reduces blood pressure consistently throughout the 24-hour period following intake. Consequently, more than any other ACE inhibitor, it is a true once-a-day antihypertensive drug. This feature can be translated into patient benefit in daily practice where the patient compliance can be improved by using once daily regimens. Further, a long acting compound can cover properly the interval between 2 intakes, which often varies. In addition increasing evidence suggests that alleviating the 24 hour blood pressure load consistently is a desirable goal to prevent the occurrence of complications and further damage of the "target organs" in hypertensive patients.

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Effects of Trandolapril on Vascular Morphology and Function During the Established Phase of Systemic Hypertension in the Spontaneously **Hypertensive Rat**

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The aim of this study was to determine the morphologic and functional vascular changes occurring following 4 weeks of treatment with the angiotensin-converting enzyme inhibitor trandolapril in the spontaneously hypertensive rat (SHR) in the established phase of hypertension. At the dosage used, 0.4 mg/kg orally, trandolapril decreased blood pressure of the SHR by 15-18% compared with that of the control animals. Immediately before the end of treatment, the following changes from control values were observed: (1) 9, 11, and 12% reductions for myocardial hypertrophy and the media thickness of the thoracic aorta and femoral arteries, respectively; and (2) an increase in the compliance of the resistance arteries, demonstrated by a shift to the right of the in vitro tension-diameter curves and a significant 22% increase in their normalized internal diameter, while their maximum contractile ability was significantly decreased. Following discontinuation of treatment, blood pressure levels remained significantly lower in the treated versus the control groups for up to 4 weeks after the last administration. At that time measurement of the studied parameters showed: (1) a rapid reversion to control values of the compliance of the resistance vessels; and (2) a slower progression, but in the same direction, in the parameters of cardiac and vascular hypertrophy. Thus, trandolapril, administered for a short period in the adult SHR, was able to reverse the cardiac and vascular morphologic changes present in this model of hypertension.

Like the effect on blood pressure, these effects were slowly reversible at the end of treatment, whereas the functional consequences at the resistance artery level seemed to display a more rapid reversibility.

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he evolution of blood pressure in the spontaneously hypertensive rat (SHR), a widely used model of genetic hypertension, is characterized by two phases. 1-3 The development phase of systemic hypertension occurs in young SHRs, i.e., from birth to 16-20 weeks of age and is accompanied by a progressive increase in blood pressure due to a strong increase in peripheral vascular resistance. During this phase, hypertrophic changes in the vascular morphology progressively appear, thus creating a structural factor that has been proposed to be related to arterial pressure via a positive feedback process.⁴ Moreover, an abnormal or "reinforced" hypertrophic response to the increased intraarterial pressure and the influence of 1 or several agents causing hypertrophy directly are likely to be contributive factors to these vascular changes.^{5,6}

In the established form of hypertension, i.e., in animals > 16-20 weeks of age, this process of vascular structural adaptation entirely dominates the hemodynamic pattern of the disease.^{4,7} Vascular changes are characterized by a increase in wall-to-lumen ratio due to smooth muscle cell hypertrophy and/or hyperplasia and connective tissue development. 6-9 Regarding myocardial hypertrophy, the adaptive response includes myocytic hypertrophy and accumulation of collagen within the interstitium. 10,11

Several studies have confirmed that angiotensinconverting enzyme (ACE) inhibitors, when administered chronically for short or long periods to

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young SHRs, are very effective in controlling the progressive increase of blood pressure and in limiting myocardial and vascular hypertrophy. 12-18 Moreover, these drugs exhibit a remarkable ability to maintain blood pressure at a low level after discontinuation of treatment. 12-16,18 However, when administered to SHRs in the established phase of hypertension, the effects of these drugs are less well documented. 15,19 Particularly, the ability of the ACE inhibitors to cause regression of the cardiovascular changes that are present in this phase have not yet been thoroughly investigated.

Thus, the present study was designed to determine the effects of short-term treatment with trandolapril, a new nonsulfhydryl converting enzyme inhibitor, 20,21 on the cardiac and vascular changes present in the SHR in its established phase of hypertension.

METHODS

Animals and treatments: Male SHRs (330–350 g; Iffa-Credo; L'Arbresle, France) were received in our laboratory at the exact age of 20 weeks. They were housed under standard conditions: 5 animals per cage, 12 hour light/dark cycle with artificial light, temperature 24 ± 1°C, tap water and food (UAR; France) ad libitum. The animals were randomized into 3 groups, each comprising 30 animals aged 21 weeks old. They then entered a 4-week regimen in which they received by daily gavage either distilled water (in a volume of 10 mL/kg; control group) or 0.4 mg/kg of trandolapril (Roussel-Uclaf, Romainville, France) dissolved in distilled water (10 mL/kg; trandolapril-treated group).

General organization of the study: Treatments were started at day 0, with subgroups comprising an equal number of control and trandolapriltreated animals. The beginning of the treatment was staggered from one subgroup to the next so that the treatment duration was the same for all the animals in relation to the experimental requirements. A first series of measurements, defined as M₁, was done immediately before the discontinuation of treatment, i.e., on day 28, in 10 animals each from the control and the trandolapril-treated groups. The blood pressure of the remaining animals was monitored weekly in a random sample of 10 animals from each group selected at the beginning of the experiment. This operation was done during treatment and during 4 weeks after its withdrawal. When the blood pressure figures had reached values half-way between those measured at day 0 and those measured at day 28, a second series of measurements, M2, was undertaken (on day 42, i.e., 2 weeks after treatment discontinuation) in 10 animals from each group. Finally, a third series of measurements, M3, was carried out when the blood pressure figures of the animals previously treated with the ACE inhibitor were no longer significantly different from those of the control group. This series of measurements was done on day 63, i.e., 5 weeks after treatment discontinuation.

General measurements: In conscious animals, the body weight, systolic blood pressure, and heart rate were monitored weekly in a population of 10 animals chosen randomly from each group and numbered. These animals were killed at the end of the experiment, during the M₃ measurement period, i.e., 1 week after the last blood pressure measurement by the plethysmographic method.²² During the M_1 , M_2 , and M_3 measurement periods, the following parameters were determined successively each day in 1 animal from each group: intraarterial measurement of systolic, diastolic, and mean blood pressures in the femoral artery in the anesthetized animal; heart weight; passive and active vascular properties in a preparation of mesenteric resistance arteries by means of an isometric myograph^{23,24}; and vessel wall hypertrophy (for this, vascular samples were taken from various levels and then fixed for histologic examination).

In vivo measurements: At the time of measurement (M₁, M₂, or M₃), animals were anesthetized with sodium pentobarbitone (45 mg/kg intraperitoneally; Clin-Midy, France). Blood pressure was measured at the left femoral artery level using a rigid catheter (Teflon, Denucath 3F; Plastimed) connected to a pressure transducer (RP 1500, Narco-Bio Systems). The signals from this pressure transducer were amplified and recorded in a polygraphic recorder (Physiograph MK 3, Narco-Bio Systems). The systolic (SBP) and diastolic (DBP) blood pressures were determined from the femoral pressure tracing. The mean blood pressure (MBP, mm Hg) was calculated from the values of the systolic and diastolic pressure by the formula: MBP = [DBP + (SBP - DBP)/3]. The differential pressure was calculated as (SBP - DBP).

In vitro measurements: Immediately after blood pressure measurements, sections of mesenteric resistance arteries were taken from the animals for in vitro study of vascular function and histologic examination. A segment of homogeneous diameter and 0.8-1 mm in length was sectioned from a second-order branch of the principal mesenteric artery. The segment was then mounted

in the isometric myograph. After mounting, vessels were kept in a Teflon-coated bath (20 mL) filled with a warmed (37°C) and oxygenated (5% CO₂ in O_2) modified Ringer's solution containing (in mM): NaCl, 119; KCl, 4.7; CaCl₂, 2.5; MgSO₄, 1.2; NaH-CO₃, 25; KH₂PO₄, 1.2; EDTA, 0.026; glucose, 5.5, adjusted to pH 7.4.

The passive properties of the preparations were determined after a period of stabilization of 45-60 minutes following their mounting in the myograph, by performing extension curves, according to a previously published protocol.25 For all the preparations, the relation between the internal diameter and the parietal tension could be represented by an exponential type of curve with the following equation:

$$T = T_0 \times 10^{\beta D}$$

where T represents the wall tension (mN/mm); T_0 (mN/mm) and β (μ m⁻¹) are constants; and D represents the internal diameter (µm).

From the equations of the extension curves determined for each of the preparations, mean curves were calculated by introducing into these equations theoretical internal diameter values, ranging from 100 µm to 300 µm in increments of 20 µm. The results of the compliance studies are therefore illustrated by these mean extension curves. The normalized internal diameter (NID, µm) was defined for each preparation from the experimental data by the intersection of the extension curve with Laplace's straight isobar with, for the slope, a pressure of 100 mm Hg.8,24,25

In a second set of experiments, preparations were set up at $0.9 \times NID$ and the active contractile properties of the vessels were then investigated by constructing a concentration-contractile relation in response to norepinephrine in the presence of cocaine 3 µM. From this preparation 2 parameters were determined: the EC₅₀ (in μM , the concentration of norepinephrine causing a half-maximal response), and the effective active pressure (EAP, kPa), the intraluminal pressure that the arterial segment can oppose at the maximum response.8,25 The EAP is calculated from Laplace's law by the formula:

$$EAP = T/r$$

where T (mN/mm) is the active tension measured during the maximum contractile response and r is the normalized radius, i.e., $(0.9 \times \text{NID})/2 \text{ (mm)}$.

Cardiac and vascular morphologic parameters: From the heart weight, the ratio of heart weight to body weight (mg/g) was then calculated and used as an index of cardiac hypertrophy. Following the cardiac sample, vascular samples were taken from each animal from the aortic arch, femoral artery, and mesenteric resistance artery. In this latter case, vessel was removed from an area as close as possible to that from which the vessel used for the functional study had been taken. After rinsing with physiologic saline solution, the samples were fixed for 24 hours in a fixative solution containing 4% paraformaldehyde and 2.5% glutaraldehyde in a 0.68 M phosphate buffer. At the end of this fixation period, the samples were then stored in a phosphate-buffered saline (Mérieux, France) containing 2.5% glutaraldehyde. For the histomorphometric study, samples were postfixed in 1% osmium tetroxide in phosphate buffer, dehydrated in increasing concentrations of ethanol, and coated longitudinally in Epon 812 resin. Sections were then taken from the samples with a glass knife (Ultrotome III; LKB). Sections of 1 µm thickness comprising the entire circumference of the preparations were mounted on glass slides for morphometric analysis with a light microscope.

Measurements were taken by means of an image processor (IBAS; Zeiss-Kontron), creating automatic segmentations of the media under operator control. A notional mean diameter of the vessels was calculated at a 4-fold magnification by measuring the diameters defined by the internal and external elastic laminae respectively and calculating the mean. The thickness was defined as the ratio between the surface of a sector of media and the length of the mean arc of this sector. The mean thickness of the complete media was converted to a 10-fold magnification by measuring the respective thicknesses of 4 sectors of media.²⁶

Statistics: All values reported in the figures and tables are expressed as means ± standard error of the mean. For each parameter, a 2-way analysis of variance was performed using the Super-ANOVA software (Abacus Concept, USA), the first factor being the period and the second being treatment. The significance of any differences is indicated in the tables by giving the values of p-treatment and p-age. When a significant p-treatment value was obtained, a comparison of the values measured at a given age in the 3 groups was performed by means of a post hoc Student-Newman-Keuls' test. When the level of p-interaction was significant, indicating that the animals reacted differently to treatment in the successive measurement period, a Student's t test was applied to the data from a given period, comparing treated versus control rats.

TABLE I General and Hemodynamic Parameters in the Control and Trandolapril-Treated Rats at the Three Measurement Periods in Anesthetized Animals

	Period			ANOVA		
	M ₁	M ₂	M ₃	p-Period	p-Treatment	p-Interaction
Body weight (g)		The same of	177 Jan 198			
C	$354 \pm 10 (10)$	$372 \pm 10 (10)$	$382 \pm 12 (9)$	NS	NS	NS
T	$357 \pm 6 (10)$	$373 \pm 6 (10)$	389 ± 7 (9)			
MBP (mm Hg)						
C	192 ± 5 (10)	$193 \pm 5 (10)$	199 ± 5 (10)	< 0.001	< 0.001	< 0.05
T	157 ± 5* (10)	179 ± 7 (8)	$195 \pm 4 (10)$			
Diff.BP (mm Hg)						
С	64 ± 3 (10)	$66 \pm 4 (10)$	68 ± 4 (10)	< 0.05	< 0.01	NS
T	$54 \pm 4 \dagger (10)$	$54 \pm 2 \dagger$ (8)	66 ± 3 (10)			
HR (beats/min)						
С	$358 \pm 7 (10)$	$348 \pm 8 (10)$	361 ± 8 (10)	NS	NS	NS
T	372 ± 8 (10)	360 ± 11 (8)	361 ± 16 (10)			

*p < 0.001; †p < 0.001.
Values are mean ± SEM; number of rats in parentheses. Two-way analysis of variance was used to determine significance of effects of period, treatment, and interaction. At a given period, the Student-Newman-Keuls' test was used to determine significance of differences between groups, except for MBP, where groups were compared using Student's t test.

C = control group; Diff.BP = differential blood pressure (SBP – DBP); HR = heart rate; MBP = mean blood pressure; T = trandolapril-treated group.

RESULTS

ramic parameters: Table I shows that body weight was not affected by ACE inhibitor treatment. Concerning systolic blood pressure measured in conscious animals, Figure 1 shows that trandolapril induced an early significant decrease (approximately 12%) of this parameter in the treated group at the end of the first week of dosing and that this effect remained present during the treatment period. When treatment was withdrawn, blood pressure progressively increased but still remained significantly lower, compared with controls, for at least 4 weeks after treatment discontinuation. Table I shows that mean blood pressure measured in

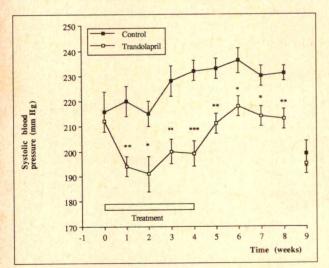
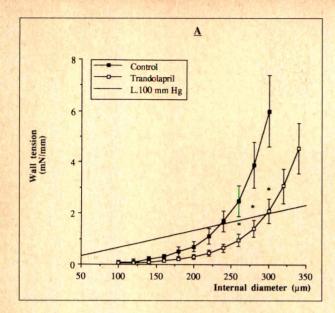


FIGURE 1. Evolution of systolic blood pressure in awake control (\blacksquare) and trandolapril-treated (\square) animals. Values are expressed as mean \pm standard error of the mean. Bar indicates treatment period. Values significantly different from controls: *p <0.05; **p <0.01; ***p <0.001. Separate points at 9 weeks indicate values of systolic blood pressure measured in anesthetized animals (\blacksquare 3).

anesthetized animals was significantly decreased during trandolapril treatment (-18%) and up to the M_2 period (-7%, i.e., a value halfway between the values at the M_1 and M_3 periods). Moreover, the evolution of this parameter observed with aging (by measurement period, p <0.001) was also significantly affected by treatment (p-interaction, p <0.05). Differential blood pressure was also significantly decreased by trandolapril at the M_1 and M_2 periods (-15% and -18%, respectively), whereas heart rate was not modified during the entire investigation period.

Effects of treatment on functional vascular parameters: For passive vascular properties, Figure 2 shows the evolution of the extension curves obtained at the 3 measurement periods. At the end of the treatment, trandolapril induced a significant shift of the extension curve to the right, compared with that of control. This effect disappeared 2 weeks after treatment withdrawal, as evidenced by the absence of displacement of the treated compared with the control curves. Further, a reverse situation was observed at the M₃ period, where the extension curve of arteries taken from previously trandolapril-treated animals were positioned to the left of the control curve. The treatmentinduced variations in NID, as shown in Table II, confirmed this evolution. ANOVA showed that treatment induced no significant change in NID along the measurement period (p-treatment, difference not significant) but significantly modified its evolution as a function of time (p-interaction, p < 0.01). This was due to an increase of this parameter at period M_1 (+22%, p <0.05, Student's t test), no difference at period M_2 , and a decrease at period M_3 (-12%, p < 0.05, Student's



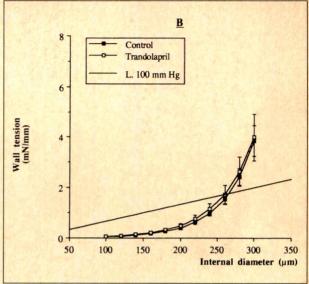
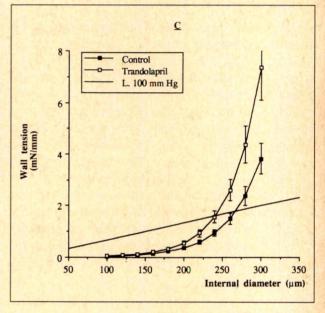


FIGURE 2. Passive extension curves of control () and trandolapril-treated () spontaneously hypertensive rat mesenteric resistance arteries at the M₁ period (after 4 weeks of treatment, A), at the M2 period (2 weeks after treatment discontinuation, B), and at the M₃ period (5 weeks after treatment discontinuation, C). Values are expressed as mean ± standard error of the mean. L.100 mm Hg is the Laplace isobar, linking wall tension to internal diameter for an intraluminal pressure of 100 mm Hg. Intersection of the isobar with the extension curves determines the normalized internal diameter (see Methods for details). Values significantly different from controls: *p < 0.05.



t test). Concerning EC₅₀ values, Table II shows that sensitivity to norepinephrine was not modified by treatment. Finally, a significant reduction of effec-

tive active pressure was observed at the end of the treatment $(M_1, -26\%)$ and persisted for up to 2 weeks after treatment withdrawal $(M_2, -17\%)$.

TABLE II Functional Vascular Parameters in the Control and Trandolapril-Treated Rats at the Three Measurement Periods

	Period				ANOVA	ANOVA		
	M ₁	M ₂	M ₃	p-Period	p-Treatment	p-Interaction		
NID (μm)	THE PROPERTY OF THE PARTY OF TH			Value of the second	HAND TO ST	TO THE REAL PROPERTY.		
C	246 ± 17 (10)	272 ± 7 (10)	274 ± 9 (10)			< 0.01		
T	$300 \pm 17*$ (10)	273 ± 13 (8)	241 ± 10* (10)					
EC ₅₀ (μM)								
C	0.51 ± 0.06 (7)	0.46 ± 0.07 (7)	0.42 ± 0.05 (9)	NS	NS	NS		
T	0.47 ± 0.09 (9)	0.51 ± 0.09 (8)	$0.40 \pm 0.04 (10)$					
EAP (kPa)								
C	32.1 ± 0.9 (7)	32.7 ± 3.1 (6)	31.3 ± 3.3 (6)	NS	< 0.01	NS		
T	$23.6 \pm 1.6 \dagger$ (9)	$27.0 \pm 1.7 \pm (8)$	27.7 ± 2.9 (8)		0.01			

*p < 0.05; †p < 0.001; ‡p < 0.001.

Values are mean ± SEM; number of rats in parentheses. Two-way analysis of variance was used to determine significance of effects of period, treatment, and interaction. At a given period, the Student-Newman-Keuls' test was used to determine significance of differences between groups, except for NID, where groups were compared using Student's t test.

C = control group; EAP = effective active pressure; EC₅₀ = effective concentration 50 of norepinephrine; NID = normalized internal diameter; T = trandolapril-treated group.

TABLE III Cardiac and Vascular Morphological Parameters in the Control and Trandolapril-Treated Rats at the Three Measurement Periods

	Period			ANOVA		
	M ₁	M ₂	M ₃	p-Period	p-Treatment	p-Interaction
HW/BW (mg/g)	Marie Walley			TAKE SE		
C	3.55 ± 0.10 (9)	3.53 ± 0.1 (10)	3.54 ± 0.05 (10)	NS	< 0.01	NS
T	$3.24 \pm 0.06*$ (9)	$3.38 \pm 0.07 \dagger$ (8)	$3.38 \pm 0.04*(10)$			
AMT (µm)						
C	103.8 ± 2.2 (10)	106.6 ± 1.9 (10)	107.8 ± 1.2 (10)	< 0.01	< 0.001	NS
T	$92.7 \pm 1.9*$ (9)	$95.9 \pm 1.2 \ddagger$ (8)	102.6 ± 2.5 (10)			
FMT (µm)						
C	72.3 ± 2.0 (9)	67.6 ± 1.9 (9)	71.3 ± 2.7 (10)	< 0.05	< 0.05	NS
T	$63.9 \pm 2.7 \dagger$ (9)	$60.9 \pm 2.0 \dagger$ (6)	71.7 ± 1.3 (8)			
RAMT (µm)						
C	ND	15.4 ± 0.9 (8)	17.1 ± 0.7 (10)	NS	NS	NS
T	ND	15.1 ± 0.8 (6)	16.2 ± 1.0 (7)			

*p < 0.01; †p < 0.05; ‡p < 0.001.
Values are mean ± SEM; number of rats in parentheses. Two-way analysis of variance was used to determine significance of effects of period, treatment, and interaction. At a given period, post hoc Student-Newman-Keuls' test was used to determine significance of differences between groups.

AMT = arotic media thickness; C = control group; FMT = femoral media thickness; HW/BW = heart weight-to-body weight ratio; ND = not determined; RAMT = resistance artery media thickness; T = trandolapril-treated group.

Effects of treatment on cardiac and vascular morphological parameters: Table III shows the effects of trandolapril on cardiac and vascular hypertrophy. Cardiac hypertrophy, measured as heart weight-to-body weight ratio, was significantly reduced and remained so over the complete period of investigation (reductions of 9, 4, and 4% for the M₁, M₂, and M₃ periods, respectively). Aortic wall and femoral wall thicknesses were also significantly reduced at the end of the treatment (-11% and -12%, respectively) and 2 weeks after its withdrawal (-10% for both), but this effect had completely disappeared 3 weeks later (M₃ period). No effect due to treatment was observed at the mesenteric resistance artery level at the M₂ or M₃ periods.

DISCUSSION

Several studies have confirmed that the SHR exhibits a certain number of physiopathologic features in common with those observed in human hypertension, particularly as regards cardiac and vessel wall hypertrophy.3,27-30 In the established phase of hypertension, which occurs in the SHR at about 20 weeks of age, the progression in the hemodynamic changes and the morphologic and functional changes of the cardiovascular effectors is very much slower than during the prehypertensive phase. 1-3,27 In this context, administering drugs to SHRs during the established phase represents a good model of the clinical situation, where patients undergo treatment when they are already hypertensive. Since it is now largely conceded that normalization of structural cardiovascular changes is an important therapeutic goal in antihypertensive strategy, it therefore appears important to define the extent to which a new antihypertensive drug is likely to interfere with these physiopathologic processes and even to reverse them.

Thus, the present study was carried out to examine the effects on blood pressure, cardiac hypertrophy, and functional and morphologic vascular properties of trandolapril, when this agent is administered in a short-term treatment in the SHR in the established phase of hypertension.

The dosage used in this study—0.4 mg/kg/day was chosen to reduce blood pressure moderately. Thus, the reduction obtained at the end of treatment (M₁ period, Table I) was 18%, an effect that was similar to that achieved under similar experimental conditions in a previous experiment.²¹ When treatment was withdrawn, blood pressure increased quickly during the first 2 weeks, but plateaued thereafter, at a level that remained significantly lower compared with control levels up to 4 weeks after this period. It finally reached control level 5 weeks after treatment discontinuation. These results are in agreement with previous observations, which reported that the persistence of the blood pressure lowering effects of the ACE inhibitor perindopril after treatment withdrawal is of relatively short duration, when administered in adult (20–24 weeks old) SHRs¹⁶ or in stroke-prone SHRs (6–10 months old). 19 Concerning differential blood pressure (SBP - DBP), which may be considered as an index of the damping property of aorta and large conduit arteries, this parameter was reduced during treatment with trandolapril and for 2 weeks after treatment withdrawal. Since cardiac output is not modified by ACE inhibitors, 16,18,31 it is likely that this reduction of pulse pressure is merely related to a vascular effect, due to an

increase of large arteries compliance by the drug. This effect has also been reported with this drug in hypertensive patients³² and with other ACE inhibitors, either in animals³³ or in healthy volunteers,^{34,35} as well as in patients with hypertension³⁶ or cardiac insufficiency.³⁷

Heart rate was not modified by trandolapril, as is now well established in experiments with drugs belonging to this pharmacologic group. 12,13,18

Concerning functional vascular parameters, trandolapril treatment induced a significant increase in the normalized internal diameter of the mesenteric resistance arteries. This effect has already been observed in previous studies in which ACE inhibitors were administered to young rats to prevent development of genetic hypertension. 12-14,16 Since media thickness was not measured in our study just before treatment cessation, it is difficult to determine if this effect was due to a decreased media thickness or a change in the intrinsic elastic properties of the vessel wall. However, it has been proposed from previous experiments that treatment with ACE inhibitors decreases the wall-tolumen ratio by a decrease in wall thickness and an increase in lumen, with no concomitant change in the media cross-section area. 12,14 It must be pointed out that this effect did not persist after treatment withdrawal, but even showed a tendency to reverse at the M₃ period, when blood pressure levels of the 2 groups were not significantly different. This would indicate that the lumen of arteries from animals previously treated with trandolapril had reversed to a lower value. At the present time, we cannot speculate on the cause of this effect.

In terms of sensitivity to pressor substances, the absence of significant change of EC₅₀ values for norepinephrine suggests that trandolapril treatment does not alter the sensitivity of mesenteric resistance arteries to this substance, in accord with results obtained in other studies after ACE inhibition in young SHRs. 12,13,16 On the contrary, the contractile ability of the arteries was decreased during treatment and 2 weeks following its withdrawal, as evidenced by the reduction in the effective active pressure at the M₁ and M₂ periods. This phenomenon, which has already been observed in previous experiments with other various agonists, 12,14,15,38 is likely to be due to an increase in the wall-to-lumen ratio of the SHR arteries and a subsequent reduction of the geometric hyperreactivity.

Finally, when considering the cardiac and vascular morphologic parameters, our results show that a short 1-month period of treatment with trandola-

pril was sufficient to cause regression of the hypertrophy present at the cardiac and vascular levels in the SHRs. The more long-lasting effect was observed for the heart, where a significant 4.5% decrease in heart weight to body weight ratio was still present when effects on blood pressure had subsided. The vascular effects appeared to be more transient than the cardiac: aorta and femoral wall thicknesses were significantly reduced only during treatment and 2 weeks after its cessation; as for the wall thickness of resistance arteries, no significant reduction was observed, at least during the period following treatment withdrawal. These results suggest that the heart is more susceptible than arteries to the hypertrophy-reducing effects of trandolapril. Moreover, these effects appear to be more marked in the conduit as opposed to the resistance arteries. An explanation of this latter observation could be that large arteries undergo mainly smooth muscle cell hypertrophy and polyploidy,6 whereas cell hyperplasia is observed at the resistance artery level. 6,39 Since it has been shown that ACE inhibitors can effectively reduce smooth muscle cell hypertrophy and polyploidy, 6,40 a greater reduction of media thickness could be expected in large as opposed to resistance arteries.

Altogether, these results show that trandolapril, administered for 1 month to SHRs in their phase of established hypertension, is able to reverse the morphologic alterations observed in the conduit and resistance arteries. These morphologic changes are responsible for functional changes, namely, improvement of compliance, which leads to a reduction of pulse pressure and decrease in contractility, thus leading to an in vivo reduction of geometric hyperreactivity. However, our data show that these changes are short-lasting (approximately 1 month) when administered in the established phase of hypertension to adult SHRs, compared with the much longer lasting effects (up to 4-5 months) observed after withdrawal of ACE inhibitor treatment when this was initiated in young SHRs to prevent the development of genetic hypertension. 12-16,18 Thus, our results confirm previous observations showing that when ACE inhibitor treatment is instituted in the presence of established vascular morphologic alterations in the SHR, significant long-term effects, either on blood pressure levels or on regression of cardiovascular changes, are much more difficult to obtain. 15,16,38

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Beneficial Effects of Trandolapril on Experimentally Induced Congestive Heart Failure in Rats

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Angiotensin-converting enzyme (ACE) inhibitors have been shown to prolong life expectancy in patients with congestive heart failure. In order to determine the relative contributions of the different factors involved in this beneficial effect, we investigated in an experimental model of postinfarction cardiac insufficiency in the rat over a 9-12-month period (1) the kinetics of the development of the hemodynamic, biologic, and morphologic alterations that accompany heart failure, and (2) the kinetics of the effects of a new, long-acting ACE inhibitor, trandolapril. Following induction of infarction, systolic blood pressure, left ventricular dP/dt, and end-diastolic pressure were immediately decreased, decreased, and increased, respectively, and these modifications persisted throughout the study. Cardiac index. on the other hand, was only initially and transiently decreased. Cardiac remodeling (left ventricular dilation, myocardial hypertrophy, and fibrosis) occurred as early as 7 days after infarction and worsened throughout the study. Plasma atrial natriuretic factor (ANF) and urinary cyclic guanosine monophosphate (cGMP) were also increased. In this model, a 1-year oral treatment with trandolapril resulted in early hemodynamic and biologic beneficial effects (reductions in preand afterload, increase in cardiac index, and decrease in plasma ANF), and in a delayed reversal of the infarction-induced cardiac morphologic alterations. Hence, the trandolapril-induced increase in survival rate is due initially to the drug's hemodynamic effects and over the long-term to

both its hemodynamic and cardiac morphologic (limitation of remodeling) effects.

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ngiotensin-converting enzyme (ACE) inhibitors have been shown to prolong life expectancy in patients with congestive heart failure, 1,2 but also in rats with postinfarction congestive cardiac insufficiency, 3-5 an experimental model widely used to investigate the effects of pharmacologic interventions. In this experimental model, the hemodynamic, 6-9 hormonal, 10 and morphologic 11,12 alterations have been independently investigated. However, their kinetics are not known, their relations remain speculative, and their relative contributions to mortality have not vet been elucidated. Therefore, the present study was undertaken in order to (1) establish the kinetics of the hemodynamic, hormonal, and morphologic modifications that occur during the development of postinfarction congestive heart failure in rats, and (2) investigate the effects of trandolapril, a new, long-acting ACE inhibitor, on these kinetics, in order to determine the factors through which these drugs work to prolong survival.

METHODS

General: Ligation of the left coronary artery was performed in 10-week-old male Wistar rats, as previously described.^{6,13} At 7 days after surgery, the surviving rats with electrocardiographic signs of myocardial infarction (MI) were housed 5 per cage, fed ad libitum with standard diet, and had free access to tap water. Sham-operated (S) male Wistar rats, aged 10 weeks, were also used and housed in identical conditions. All experiments were performed in accordance with the official regulations of the French Ministry of Agriculture.

Experimental protocols: Two distinct protocols were performed.

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PROTOCOL 1: MI and S rats were randomly divided into 5 different subgroups and killed 7 days (shown as 0 month in the figures, n = 9 and 10, respectively), and 1 (n = 14 and 15), 3 (n = 16 and 15), 6 (n = 22 and 15), and 9 (n = 37 and 20) months after surgery.

At each time point (0, 1, 3, 6, and 9 months) all surviving S and MI rats were weighed and their systolic blood pressure and heart rate measured in the conscious state using a tail cuff and a photoelectric pulse detector (PC, model 139 IITC, Woodland Hills, CA). Smaller samples (n = 6-15) of S and MI rats were randomly selected and placed in metabolic cages in order to collect 12-hour urine for diuresis and urinary cyclic guanosine monophosphate (cGMP) determination ([125I]cGMP assay, Amersham, UK).

Following these hemodynamic and metabolic determinations at 0, 1, 3, 6, and 9 months, MI and S rats were anesthetized with pentobarbital (50 mg/ kg, 0.1 mL/100 g, intraperitoneally). Catheters were placed in the right femoral artery and in both carotid arteries. The right carotid catheter was advanced into the left ventricle and baseline values of systolic, diastolic, and left ventricular enddiastolic pressures (Gould DC amplifier 13-4615-10 model, Gould Instruments, Cleveland, OH), dP/dt (Gould differentiator 13-4615-71 model), and heart rate (Gould Biotach 13-4615-66 model) were recorded on a multichannel Gould polygraph (model 6610-06). Radioactive microspheres (141 Ce, $15 \pm 3 \mu m$) were diluted in 20% dextran solution, ultrasonically shaken, and injected into the left ventricle (60,000-80,000 spheres) over 10 seconds in order to determine cardiac index. A reference blood sample (0.7 mL/min for 90 sec) was withdrawn from the right femoral catheter (Harvard pump, model 901, South Natick, MA). Total radioactivity injected and radioactivity of the reference blood sample were determined in a gamma counter (Compugamma 1280 LKB, Turku, Finland).

Cardiac index was calculated as:

Reference blood sample withdrawal rate × total radioactivity injected Reference blood sample radioactivity × body weight

Total peripheral resistance was obtained by dividing mean arterial pressure by the cardiac index.

At the end of the experiments, a blood sample was collected into ethylene diaminetetraacetic acid (EDTA) plus aprotinin in order to determine plasma atrial natriuretic factor (ANF; human a ANF assay, Amersham, UK). Then the animals were killed and the heart and aorta were immediately excised, cleaned, and weighed fresh.

After fixation, both ventricles were cut into 4, 2-mm thick transversal slices, and 1 3-µm thick section was obtained from each slice and stained with Sirius red.⁵ Infarct size was expressed as the ratio of scar length to the sum of the epicardial and endocardial circumferences. Subendocardial and subepicardial collagen densities were evaluated in the viable ventricular wall of the 4 ventricular slices at a $250 \times \text{magnification from } 40 \text{ fields } (10/\text{slice})$ in the endocardium and in the epicardium.

After fixation, longitudinal and transverse specimens were obtained from each aorta and 3 3-µm thick sections were cut from each specimen, mounted on glass slides, and treated by specific staining: orcein for elastin, Sirius red for collagen, and hematoxylin after periodic oxidation for nuclei

Media thickness (between the internal and external elastic laminae, 4 × magnification), smooth muscle cell cross-sectional area, and collagen density (250 × magnification, 8 randomly selected fields) were determined on the transverse sections. Aortic nuclear density (250 × magnification) was determined in 8 randomly selected fields from the longitudinal section.

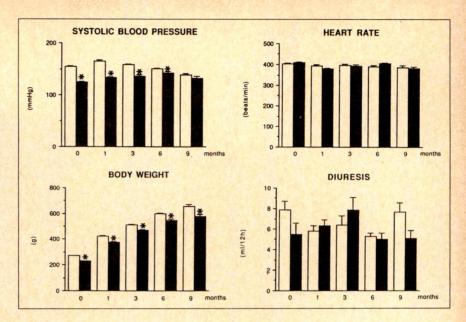
Computer-assisted morphometry was performed using a Nachet 15000 automatic analyzer (Nachet; Evry, France) connected to a microcomputer.

In the 2 subgroups of MI and S rats that were sacrificed 9 months after surgery, the date of death of the spontaneously deceased animals was recorded in order to calculate survival rate. The surviving MI and S rats were killed and the heart and aorta removed, weighed, and treated as previously described.

PROTOCOL 2: At month 0 (7 days after surgery), rats with electrocardiographic signs of MI (n = 58)were randomly assigned to MI controls (n = 28)and MI trandolapril (n = 28). Trandolapril (0.1 mg/kg/day) treatment was administered in the drinking water and lasted for 1 year.

Cages were inspected daily for dead animals, from which the heart and aorta were removed, weighed, and used for morphometric measurements (infarct size, subendocardial collagen, aortic media thickness, aortic collagen density). Systolic blood pressure, heart rate, and body weight were measured as previously described in all surviving conscious animals at 1, 3, 6, 9, and 12 months after starting the protocol. Diuresis was also measured in 8 randomly selected animals from each group.

FIGURE 1. Mean values (± SEM) of systolic blood pressure, heart rate, body weight, and diuresis determined at 0, 1, 3, 6, and 9 months in surviving sham operated (S, open bars) and myocardial infarction (MI, filled bars) rats. Value significantly different from the corresponding S value: *p < 0.05 or better.



At the end of the study, i.e., 12 months after starting the treatment, hemodynamic measurements (systolic and diastolic blood pressures, heart rate and cardiac output; radioactive microspheres technique) and plasma ANF determinations were performed in 4 control and 5 trandolapril-treated rats, randomly selected among the surviving animals of these 2 groups (n = 8 and 11, respectively).

Statistical analysis: All reported values are given as mean ± standard error of the mean.

In protocol 1, for all parameters measured in conscious and killed S and MI animals, a 2-way analysis of variance was performed, testing the effects due to cardiac insufficiency, time, and the interaction between disease and time. Correlations were investigated (1) in spontaneously deceased MI rats, between survival duration and cardiac morphologic parameters, and (2) in killed MI rats

between hemodynamic and cardiac morphologic parameters.

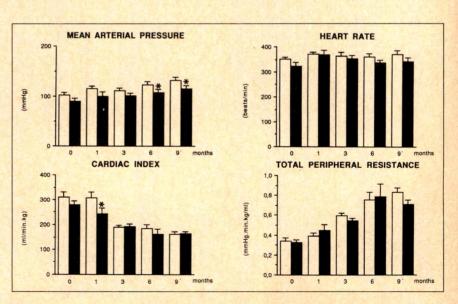
In protocol 2, histomorphologic parameters from spontaneously deceased animals were pooled into 4 groups, based on their deaths occurring in the 0–3, 3–6, 6–9, and 9–12 months following coronary ligation.

For all of the investigated biologic, hemodynamic, or histomorphologic parameters, the effects of trandolapril were assessed using a 1-way analysis of variance.

RESULTS

Protocol 1: SURVIVAL: In the subgroup of MI rats that was followed for 9 months, the spontaneous deaths recorded allowed the calculation of a median survival time of 235 days.⁵ In the subgroup

FIGURE 2. Mean values (± SEM) of mean arterial pressure, heart rate, cardiac index, and total peripheral resistance determined at 0, 1, 3, 6, and 9 months in the anesthetized sham operated (S, open bars) and myocardial infarction (MI, filled bars) rats just before sacrifice. Value significantly different from the corresponding S value: *p < 0.05 or better.



of 75 S rats no death occurred over the 9-month observation period.

HEMODYNAMIC PARAMETERS: Figure 1 compares systolic blood pressure, heart rate, body weight, and diuresis in MI and S rats. As can be seen, body weight was always significantly lower in MI than in S rats (deficit of 8-12%), and up to 6 months, systolic blood pressure was also significantly lower in MI than in S rats. Regarding systolic blood pressure, there was an interaction between cardiac insufficiency and time, and the significant difference between MI and S rats progressively decreased with time. Heart rate and diuresis were identical in MI and S rats throughout the study.

Figure 2 illustrates the evolution with time of mean arterial pressure, heart rate, cardiac index, and total peripheral resistance in MI and S rats. Mean arterial pressure increased with age in both groups but always remained lower in MI than in S rats and significantly so at 6 and 9 months. Heart rate values were identical in MI and S rats. Cardiac index values decreased with age in both S and MI rats and were significantly lower in MI rats at 1 month only. Total peripheral resistance values increased progressively with age in both groups and were never significantly different from each other.

Figure 3 illustrates the evolution with time of left ventricular dP/dt, left ventricular end-diastolic pressure, urinary cGMP, and plasma ANF. The dP/dt values were always lower in MI than in S rats and significantly so at 1 and 6 months, whereas left ventricular end-diastolic pressure values were at all ages greater in MI than in S rats and significantly so at 3 and 6 months.

BIOLOGIC PARAMETERS: Urinary cGMP values decreased with age in both groups but were always significantly higher in MI than in S rats. Plasma ANF was significantly higher in MI than in S rats at 3 and 6 months but no longer so at 9 months (Figure 3). For both urinary cGMP and plasma ANF, there was a significant interaction between disease and age.

MORPHOLOGIC PARAMETERS: Mean value of infarct size calculated in all spontaneously deceased or killed MI rats was $38 \pm 1\%$, and there was no significant difference between the 5 subgroups.

Figure 4 illustrates the evolution with time of the cardiac histomorphologic parameters in killed animals. Heart weight and heart weight/body weight ratio increased and decreased, respectively, with age in both groups. The heart weight/body weight ratio was negatively correlated with age in both killed MI (y = -0.00375x + 3.91; r = 0.441; p < 0.001) and S(y = -0.00309x + 2.74; r = 0.790;p < 0.001) rats. In addition, there was no significant interaction between time and disease for heart weight and heart weight/body weight ratio. Left ventricular cavity area was significantly greater in MI than in S rats throughout the study, thus indicating ventricular dilation. Myocardial collagen density was significantly greater in MI than in S rats, and more markedly so in the endocardium than in the epicardium (not shown). Regarding left ventricular cavity area and subendocardial collagen density, there was a significant interaction between age and disease.

Figure 5 illustrates the evolution with time of the aortic morphologic parameters. For none of them was there a significant difference between MI and S rats. Aortic media thickness and smooth

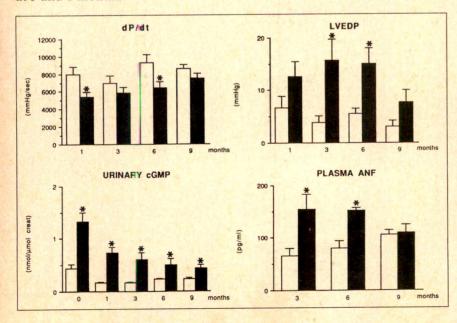
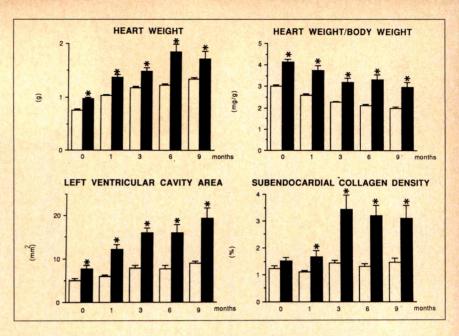


FIGURE 3. Mean values (± SEM) of dP/dt, left ventricular end-diastolic pressure (LVEDP), urinary cyclic guanosine monophosphate (cGMP), and plasma atrial natriuretic factor (ANF) determined at regular intervals in anesthetized sham-operated (S, open bars) and myocardial infarction (MI, filled bars) rats. Value significantly different from the corresponding S value: *p < 0.05 or better.

FIGURE 4. Mean values (± SEM) of heart weight, heart weight to body weight ratio, left ventricular cavity area, and subendocardial collagen density determined after sacrifice at 0, 1, 3, 6, and 9 months in sham operated (S, open bars) and myocardial infarction (MI, filled bars) rats. Value significantly different from the corresponding S value: *p < 0.05 or better.



muscle cell cross-sectional area increased with age in both groups, whereas aortic nuclear density and collagen density decreased with age.

CORRELATIONS BETWEEN SURVIVAL DURATION AND HEMODYNAMIC AND CARDIAC HISTOMORPHOLOGIC PARAMETERS: In spontaneously deceased animals, there was a significant negative correlation between infarct size and survival duration (r = 0.536; p < 0.01) and between heart weight/body weight ratio and survival duration (y = -0.0065x + 5.44; r = 0.569; p < 0.001).

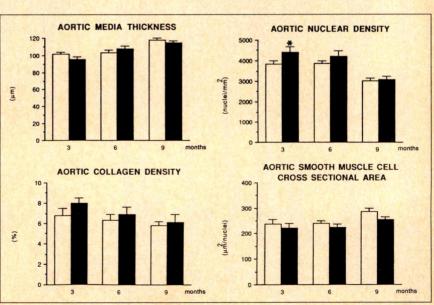
In MI animals that were killed, larger infarcts were associated with greater left ventricular end-diastolic pressure values (r = 0.330; p < 0.05). In addition, left ventricular end-diastolic pressure was positively correlated with heart weight (r = 0.557; p < 0.001), and subendocardial (r = 0.449;

p <0.001), but not subepicardial, collagen density.

Protocol 2: SURVIVAL: Trandolapril significantly improved survival rate in MI rats during the initial 6-month period. For instance, the first spontaneous death occurred after 4 and 134 days in control and in trandolapril-treated MI rats, respectively. Further, the delay after which 25% of the animals had spontaneously died was 119 and 227 days in control and in trandolapril-treated MI rats, respectively. After 9 months, there was no longer any difference between the survival curves of control and trandolapril-treated animals.⁵

HEMODYNAMIC AND BIOLOGIC PARAMETERS: Figure 6 shows that trandolapril significantly reduced the age-related increase in body weight. Trandolapril induced an early reduction (approxi-

FIGURE 5. Mean values (± SEM) of aortic media thickness, aortic nuclear density, aortic collagen density, and aortic smooth muscle cell cross-sectional area determined after sacrifice at 3, 6, and 9 months in sham operated (S, open bars) and myocardial infarction (MI, filled bars) rats. Value significantly different from the corresponding S value: *p <0.05 or better.



mately 12%) in systolic blood pressure that persisted up to 9 months. Heart rate was never drug-affected. Finally, trandolapril also induced an early, significant, and long-lasting increase in diuresis (approximately 85%).

Figure 7 shows that in the animals surviving at 12 months after treatment initiation, trandolapril significantly increased cardiac index and decreased total peripheral resistance. Trandolapril also markedly and significantly reduced plasma ANF.

MORPHOLOGIC PARAMETERS: Mean infarct sizes determined in control MI $(34 \pm 2\%)$ and in trandolapril-treated MI rats $(38 \pm 2\%)$ were not significantly different.

Trandolapril opposed the age-related increase in heart weight and decreased subendocardial collagen density throughout the study, but these effects were significant only after 6 months of treatment. Simultaneously, trandolapril slightly decreased aortic media thickness and reduced aortic collagen density, significantly so after 6 months (Figure 8).

DISCUSSION

Development of postinfarction cardiac insufficiency (protocol 1): Ligation of the left coronary artery in the rat rapidly causes a cardiac overload that progressively leads to the development of chronic congestive cardiac insufficiency in the surviving animals. The latter is characterized by left ventricular dilation, an increase in ANF secretion, a deterioration of cardiac performance, and cardiac remodeling (myocardial hypertrophy and fibrosis). In our 2 protocols, mean infarct size in control MI rats (spontaneously deceased plus killed animals) was of similar magnitude (34–38%) and very near to that reported by Pfeffer et al.³ As a result, the median survival time of control MI rats (235 days) was virtually identical to that reported in the Pfeffer's study (237 days).³ Finally, our data confirm that the larger the infarct size, the shorter the survival duration.

In this experimental model, infarction-induced cardiac insufficiency results in a dilation of both the ventricular and atrial cardiac cavities, thus causing a strong increase in ANF secretion, which stimulates cGMP production. In our experiments, urinary cGMP excretion, a noninvasive marker of plasma cGMP and hence of heart failure, ¹⁰ was strongly increased in MI rats compared with S rats. The evolution with time of plasma ANF and urinary cGMP values was comparable: after a strong initial increase in MI rats compared with S rats, the difference progressively waned. This was probably because the animals that survived the longest had the smallest infarcts and hence the

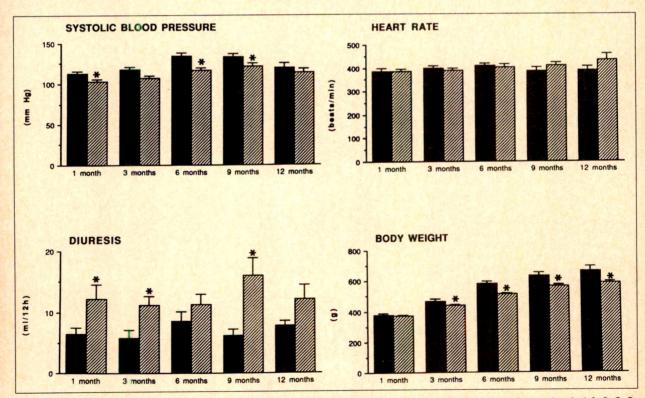


FIGURE 6. Mean values (\pm SEM) of systolic blood pressure, heart rate, diuresis, and body weight determined at 1, 3, 6, 9, and 12 months in surviving control (*filled bars*) and trandolapril-treated (*hatched bars*) MI rats. Value significantly different from the corresponding control value: *p <0.05 or better.

MEAN ARTERIAL PRESSURE CARDIAC INDEX 120 300 100 80 200 (ml/min.kg) Hg 60 E 40 100 20 PLASMA ANF TOTAL PERIPHERAL RESISTANCE 250 200 0,8 (mmHg.min.kg/ml) 150 (|m/gd) 0,6 100 0,4 50 02 0.0

FIGURE 7. Mean values (± SEM) of mean arterial pressure, cardiac index, total peripheral resistance, and plasma atrial natriuretic factor (ANF) determined at 12 months in the anesthetized control (filled bars) and trandolapril-treated (hatched bars) MI rats before sacrifice. Value significantly different from the corresponding control value:

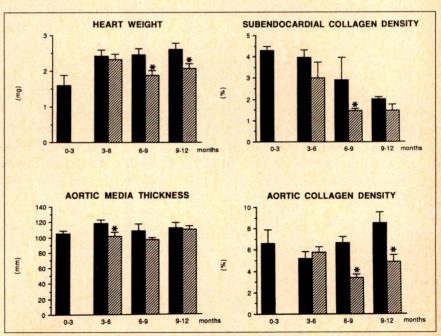
*p < 0.05 or better.

smallest degree of cardiac insufficiency. Diuresis was not significantly affected in MI rats, probably because of the release of ANF, which, by inhibiting aldosterone secretion, counteracts the water and sodium retention that occurs during decompensated heart failure.

Induction of infarction led to an immediate and significant decrease in systolic blood pressure that progressively diminished and was no longer signifi-

cant at 9 months. Different mechanisms are probably involved in this phenomenon: the activation of peripheral pressor mechanisms and the compensatory hypertrophy of the viable left ventricle, 7,14 and the fact that the decrease in blood pressure is related to the infarct size, which is smaller in the animals that survive the longest. Cardiac index was only transiently decreased 1 month after coronary ligation and recovered thereafter, whereas

FIGURE 8. Mean values (± SEM) of heart weight, subendocardial collagen density, aortic media thickness, and aortic collagen density determined in control (filled bars) and trandolapriltreated (hatched bars) MI rats spontaneously deceased in the 0-3, 3-6, 6-9, and 9-12 months. Note that no animal died spontaneously during the 0-3 month period among the trandolapriltreated MI rats. Value significantly different from the corresponding control value: *p < 0.05 or better.



total peripheral resistance was never significantly affected in MI rats. In contrast, left ventricular dP/dt and end-diastolic pressure were strongly and often significantly decreased and increased, respectively, in MI rats compared with S rats throughout the experiment, indicating cardiac failure.9

From the histomorphologic point of view, it is well established that after MI the surviving myocardium undergoes an early hypertrophic process in an attempt to normalize wall stress. However, in the long-term, this ventricular remodeling progressively becomes inadequate to maintain a normal ventricular pump performance and to normalize myocytes and diastolic wall stress. Dilation of the ventricular chamber, inadequate mural thickening, and reduced oxygen delivery contribute to maintain elevated myocardial and cellular loads, leading to progression of the disease. 9,12,15 Our data in control MI animals confirm (1) the dilation of the left ventricular cavity, a phenomenon that strongly worsened throughout the 9-month observation period, and (2) the hypertrophy of the whole heart, as shown by the larger increase of total heart weight in control MI rats compared with S rats throughout the study. The fact that the slope and intercept values of the age-heart weight/body weight ratio regression line were both greater in spontaneously deceased than in killed MI rats clearly demonstrates the deleterious role of cardiac hypertrophy. This is further confirmed by the existence of a positive correlation between heart weight and left ventricular end-diastolic pressure in our control MI rats.

Induction of MI was also associated in our experiments with an increased collagen content of the viable left ventricle, and more especially so in the subendocardium. This accumulation of collagen, which results from both excessive workload and myocardial perfusion deficit, has been shown to decrease capillary density and to increase the diffusion distance for oxygen. 16 Consequently, maximum oxygenation capacity of myocardial tissue is further decreased,11 the occurrence of arrhythmias is augmented, 14 and ultimately the risk of death is increased. The development of connective tissue also contributes to decreased ventricular compliance, a factor involved in elevated left ventricular end-diastolic pressure. Indeed, our results show a positive correlation between subendocardial collagen density and left ventricular end-diastolic pressure. Finally, it must be stressed that the cardiac remodeling process develops very rapidly in this experimental model, since left ventricular dilation, cardiac hypertrophy, and subendocardial fibrosis are significant as early as 7, 7, and 28 days, respectively, after coronary ligation.

As might be expected, no major vascular morphologic change was observed in this experimental model of heart failure. Aortic media thickness and smooth muscle cell cross-sectional area increased with age in both MI and S rats. Aortic nuclear density progressively decreased. A slight hyperplasia was observed in MI rats compared with S rats, as evidenced by the greater nuclear density and the smaller smooth muscle cell cross-sectional area. Finally, collagen density was slightly but not significantly increased in MI rats.

Effects of trandolapril (protocol 2): Trandolapril-induced prolongation of survival⁵ was accompanied by an improved hemodynamic status in the treated compared with the control MI rats. Trandolapril significantly decreased systolic blood pressure and increased diuresis as soon as treatment was initiated, and this resulted in an improved cardiac performance, as evidenced by the increased cardiac index and the decreased plasma ANF values observed in the MI rats that survived up to 12 months. Moreover, trandolapril opposed the cardiovascular remodeling that usually occurs in MI rats. It strongly prevented the deleterious development of global cardiac hypertrophy, as shown by the reduction in heart weight, and opposed the development of cardiac fibrosis, as shown by the decrease in subendocardial collagen density. These cardiac antihypertrophic and antifibrotic effects of trandolapril were delayed in their onset compared with the hemodynamic ones, for they were significant only at >6 months of treatment. However, once present, they clearly both contributed to the preservation of an adequate cardiac oxygenation, to an improved cardiac efficiency, and to the prolongation of survival. Similar antihypertrophic and antifibrotic properties were also observed with trandolapril at the vascular level, which most likely resulted in an improved aortic compliance and hence contributed to reduced mortality.5

In conclusion, our study describes the kinetics of the hemodynamic, biologic, and morphologic changes that develop after ligation of the left coronary artery in rats and assesses their relative contributions to mortality. It points out that cardiac remodeling (hypertrophy and fibrosis) is an early occurring process that proves unable to restore a normal cardiac function and that progressively leads to cardiac insufficiency. Trandolapril exerts beneficial effects on pre- and afterload and improves cardiac function. These early and longlasting favorable hemodynamic effects, and later the drug's delayed antihypertrophic and antifibrotic properties at both cardiac and vascular levels, appear to be responsible for the improved survival duration.

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Reversal of Cardiac and Large Artery Structural Abnormalities Induced by Long-Term Antihypertensive Treatment with Trandolapril

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In 15 patients with untreated mild to moderate essential hypertension and left ventricular hypertrophy, we assessed blood pressure, echocardiographic left ventricular mass index, brachial artery compliance (pulsed doppler flowmetry), and calculated forearm vascular resistance (strain gauge plethysmography) before, during (6 and 12 months) and after (1 month washout period) 1 year of satisfactory (blood pressure ≤140/90 mm Hg) antihypertensive therapy with the angiotensin-converting enzyme inhibitor trandolapril (2.0 mg orally once daily).

During the antihypertensive effective treatment, we observed a significant reduction of systolic and diastolic blood pressures, left ventricular mass index, and forearm vascular resistance at both 6 and 12 months. In addition, brachial artery compliance was significantly increased. After washout, systolic (156 ± 3 mm Hg) and diastolic (102 ± 1 mm Hg) blood pressures returned to levels comparable to baseline. However, left ventricular mass index (132 \pm 4; p < 0.01) and brachial artery compliance (1.53 \pm 0.01; p < 0.01) were still different from baseline. These results demonstrate that chronic antihypertensive treatment with trandolapril is associated with a stable regression of cardiac and vascular abnormalities, which is partially unrelated to the blood pressure lowering effect.

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lthough it has been demonstrated that large artery distensibility is impaired in essential hypertension 1 and that the acute administration of different drugs, such as calcium antagonists or angiotensin-converting enzyme (ACE) inhibitors, is able to increase brachial artery diameter and compliance,² it is still unclear whether the long-term treatment with ACE inhibitors may reverse the structural vascular changes of large arteries in patients with essential hypertension. This issue is of great interest, since large artery compliance is a major determinant of hypertensioninduced left ventricular (LV) hypertrophy, as demonstrated by the significant inverse relation existing between arterial compliance and LV mass/volume ratio, and cardiac function.³ For this reason, regression of LV hypertrophy without improvement of large artery compliance may be responsible for the marked impairment of cardiac function that takes place after the withdrawal of the antihypertensive treatment, as demonstrated by Ferrario and coworkers⁴ in experimental studies. Conversely, uniform reversal of cardiac and arterial structural changes in hypertensive patients could account for our observation that therapy withdrawal in hypertensive patients in whom the regression of LV hypertrophy has been obtained by long-term antihypertensive treatment with ACE inhibitors is not accompained by an impairment in cardiac function.⁵ Indeed, in a previous study in hypertensive patients,6 we reported that a 6-month treatment with the ACE inhibitor enalapril induces a significant improvement in large artery compliance that persists after withdrawal of the pharmacologic treatment.

Asmar and coworkers⁷ have recently reported that in patients with sustained essential hypertension, a 3-month treatment with the ACE inhibitor perindopril increases brachial artery compliance and reduces LV mass. After withdrawal of the treatment, they observed a return of large artery

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compliance toward baseline values, whereas LV mass remained decreased. This observation appears to be in contrast with the possibility that long-term antihypertensive treatment with ACE inhibitors may reverse hypertension-induced structural changes not only in the heart, but also in large arteries.

To clarify this controversial issue further, in the present study we investigated the effects of long-term antihypertensive treatment with the new ACE inhibitor, trandolapril, on cardiac and vascular anatomy and function in hypertensive patients with LV hypertrophy.

METHODS

Patients: A study population of 21 patients with previously untreated mild-to-moderate essential hypertension was recruited from the outpatient hypertension clinic of our Institute. They did not show any history or clinical evidence of coronary artery disease, diabetes mellitus, renal insufficiency, or heart failure. No patient had electrocardiographic signs of prior myocardial infarction. Further, to exclude accompanying coronary disease, patients were required to have normal wall motion as assessed by radionuclide ventriculography both at rest and during exercise. Blood pressure was > 160 mm Hg systolic or > 95 mm Hg diastolic on at least 5 consecutive readings in the outpatient clinic on different days. Blood pressure was measured with the subject in the sitting position, after a 10-minute rest in a darkened room, by means of a standard sphygmomanometer with a cuff of appropriate size, following the recommendations of the American Heart Association.8 Secondary hypertension was ruled out in all patients by laboratory and radiographic studies. All patients were fully informed about the procedures and aims of the study, and written consent was obtained by all subjects before the study. Each patient satisfied the echocardiographic criteria for left ventricular (LV) hypertrophy: i.e., Penn LV mass index ≥ 134 g/m^2 for men and ≥ 110 g/m² for women.^{9,10} The possible contribution of regular exercise to the genesis of LV hypertrophy was excluded by history. Patients had no signs, symptoms, or history of major diseases other than hypertension.

STUDY DESIGN

In control conditions all patients underwent 3 sequential studies on the same day. First, M-mode echocardiography and pulsed Doppler evaluation were performed with 2-dimensional echocardiographic monitoring, for measurement of both LV

wall thickness and dimensions in order to calculate LV mass and LV early and late peak velocity flow to measure LV diastolic function, evaluated as the early/late ratio. Second, peripheral pulsed Doppler flowmetry was performed for the determination of brachial artery compliance. Finally, straingauge plethysmography for the measurement of peripheral vascular resistance was performed. During these studies automatic blood pressure determinations were obtained by blood pressure monitor (model 9001-S; Vita-Stat Medical Service, Bellevue, Washington). Subsequently, treatment was started with trandolapril (Roussel-Uclaf), at the dose of 2 mg once a day, orally.

After 1 month of treatment, a new set of blood pressure measurements was obtained in each patient in the outpatient hypertension clinic by the same physician. Only the patients showing sitting blood pressure values ≤140/90 mm Hg were entered into the study. All patients showing a satisfactory blood pressure response to therapy returned to the outpatient hypertension clinic at 2-month intervals for a 12-month follow-up period. In the responders, sequential noninvasive studies were performed again after 6 and 12 months of effective therapy. Finally, the antihypertensive treatment was interrupted, and all patients underwent a new echocardiogram and peripheral hemodynamic evaluation after a 1-month washout period.

PROCEDURES

Echocardiographic techniques: The M-mode echocardiography was performed with the standard techniques previously reported from this laboratory. 11 In particular, echocardiograms were obtained with the patients in the partial left lateral decubitus position using a 2.5 MHz transducer (model 77020AC; Hewlett-Packard) and recorded on light-sensitive paper at a paper speed of 50 mm/sec. Images were obtained under sector scanning monitoring to detect any change in LV shape and to avoid angulation of the ultrasonic beam.11 Echocardiographic tracings were coded and read in random order by 2 expert observers blinded to the protocol and to the patient data. Differences between readers of 1 mm in measurement of interventricular septum and posterior wall thickness and of 2 mm in measurement of LV internal dimensions were averaged. Greater differences were resolved by review of the coded echocardiograms. Measurements of LV internal diameter, interventricular septum, and posterior wall thickness were made according to the Penn convention at end-diastole and end-systole. Echocardiographically measured volumes in end-diastole and endsystole were derived using the Teicholtz formula.¹² The reliability of this technique has been demonstrated.¹³ Echo LV mass was calculated at both end-diastole and end-systole according to the simple and anatomically validated formula:

LV mass =
$$1.04 \times [(S + D + P)^3 - D^3] - 13.6$$

where S is the interventricular septum thickness, D is the LV internal diameter, and P is the posterior wall thickness. To minimize the impact of variation of body size on LV mass, it was corrected for body surface area. Stroke volume was derived as the difference between end-diastolic and end-systolic volume, and cardiac output by multiplying stroke volume by heart rate, as derived by the echocardiogram. Total peripheral resistance was calculated by dividing mean arterial pressure (calculated as diastolic arterial pressure plus one-third of the pulse pressure) for cardiac output and multiplying × 80). End-systolic stress was calculated according to the following formula:

$$0.98 \times [(0.334 \times D_{ES} \times Pr)/P_{ES} \times (1 + P_{ES}/D_{ES})] - 2$$

where D_{ES} is the LV internal diameter at endsystole, Pr is systolic blood pressure, and P_{ES} is the LV posterior wall thickness at end-systole. Diastolic function of the left ventricle was evaluated by the measurement of the peak early and late velocity flow through mitral valve with pulsed Doppler echocardiography technique (early/late ratio).¹⁴

Peripheral two-dimensional pulsed Doppler **flowmetry:** Following the measurement of forearm volume by water displacement, the subjects were placed in the recumbent position with the right arm supported at the midthoracic level in a room with a controlled temperature of $23 \pm 1^{\circ}$ C. The forearm arterial circulation was studied noninvasively by means of a bidimensional pulsed Doppler system (Alvar Electronics, Montreuil, France) and the probe was fixed with a stereotaxic device over the course of the brachial artery, as previously reported from this laboratory.6 This apparatus enables the estimation of the diameter, blood velocity, and volumetric blood flow of the brachial artery and it has been validated by Safar et al. 15 This system has 2 fundamental characteristics: a bidimensional recording of the Doppler signals and a range-gated time system of reception. With the first, using a probe containing 2 transducers and forming between them an angle of 120°, it is possible to know the angle between the ultrasonic beam and the vessel; by the second characteristic,

it is possible to select the delay from the emission and the duration of the reception and to convert this time echographically into the depth and width of the Doppler measured volume. Indeed, this technique allows determination of the diameter (d, cm), the blood velocity, and calculation of the cross-section (A, cm²) of the artery (A = π d²/4). All the determinations of arterial diameter were repeated at least twice in each patient. The variability of these determinations in our laboratory is of about 7%.

Determination of brachial artery compliance:

In all patients, omero-radial pulse wave velocity was determined by applying 2 pulse transducer heads (Ote Biomedica; Firenze, Italy) to the most prominent part of the brachial and radial arteries of the right arm. The time delay was measured between the nadirs of simultaneously recorded pulse waves at a paper speed of 150 mm/sec. The nadir was defined as the point obtained by extrapolating the wave front downward and was measured from the intersection of this line with a straight line extrapolation of the last part of the diastolic curve.⁷ Measurement of the distance between the 2 transducers was then used to calculate pulse wave velocity (PWV). This was averaged over at least one respiration cycle, that is, about 10 beats. The intraobserver variability was about 9%. Brachial artery compliance was determined according to the equation of Bramwell and Hill.^{3,7} In this equation PWV = $(V\delta P/\rho\delta V)^{1/2}$, where V = arterial volume, δV = the change in volume, δP = the change in pressure, and ρ = blood density. From this equation, it is easy to calculate the brachial arterial compliance (BAC) as BAC = $\delta V/\delta P = V/\rho PWV^2$. Since V can be expressed in terms of radius per unit length, then, $\delta V/\delta P = \pi r^2/\rho PWV^2$, where r is the inner radius of the artery. In the present equation, $\delta V/\delta P$ is expressed in cm⁴/dyne × 10⁷, and with D in cm, PWV in m/sec, and $\rho = 1.06.7$ The variability of the method was about 9%.

Plethysmographic techniques: The dominant arm was slightly elevated above the level of the right atrium and a mercury-filled Silastic strain gauge was placed about 3 cm below the antecubital fossa. A blood pressure cuff was placed on the upper arm and inflated to 40 mm Hg rapidly to occlude venous outflow from the extremity. A wrist blood pressure cuff was inflated to suprasystolic pressure 1 minute before any recordings were made, to exclude the hand circulation. Flow measurements, expressed in mL/min × 100 g, were recorded for approximately 7 seconds every 15 seconds; 5 readings were obtained for each resting

value. Vascular resistances, expressed as arbitrary units, were calculated by dividing mean arterial pressure (calculated as diastolic pressure plus 33% of the pulse pressure) by the peripheral blood flow. Serial measurements of systolic and diastolic blood pressure were obtained by means of the Vita-Stat automatic device. Blood pressure in each subject was expressed as the average value of all the measurements. Heart rate was calculated from simultaneously recorded electrocardiogram.

STATISTICAL ANALYSIS

Means + SE were calculated by standard statistical methods. Differences in values between different groups were assessed by variance analysis (F-test).

RESULTS

From a total recruited population of 21 patients, 6 were excluded from the study. One patient was excluded because of unsatisfactory blood pressure response to trandolapril, the others because they did not keep their appointments at the outpatient hypertension clinic. Therefore, the study included 15 hypertensive patients with LV hypertrophy, in whom daily administration of trandolapril induced a normalization of blood pressure (≤140/90 mm Hg). Table I summarizes the clinical characteristics of the 15 patients included in the study. Hemodynamic data recorded in control conditions at 6 and 12 months of effective treatment with trandolapril. and 1 month after withdrawal of the treatment, are shown in Figure 1. The significant reduction of systolic and diastolic blood pressure induced by the treatment was associated with a significant reduction in total peripheral resistance, since cardiac output remained unchanged (from 4.97 ± 0.2 to 5.1 ± 0.3 and 5.1 ± 0.2 L/min at 6 and 12 months, respectively). The withdrawal of therapy determined an increase in systolic and diastolic blood pressure, so that arterial pressure returned to values comparable with those recorded in control conditions. No significant changes in heart rate and stroke volume were observed throughout the study.

Effects on left ventricular anatomy and function: The accuracy of the echocardiographic measurements was demonstrated by the observation that when LV mass at end-diastole and end-systole in each echocardiographic tracing were compared, the correlation coefficient varied between 0.9 and 0.98. No change in LV shape was detected by 2-dimensional echocardiography throughout the study.

Age (years)	49 ± 2
Weight (kg)	72 ± 3
Height (cm)	163 ± 2
Forearm volume (mL)	990 ± 23
Duration of hypertension (years)	6 ± 2
Male/Female	8/7
SAP (mm Hg)	160 ± 4
DAP (mm Hg)	105 ± 1
HR (bpm)	73 ± 4
LVMi (g/m²)	153 ± 6.6

In control conditions, the mean values of LV mass index and the interventricular septal (IVS) and posterior wall (PW) thicknesses, measured at end-diastole, were above the normal range as reported by Reichek et al. 10 In contrast, LV dimensions were in the normal range (LV end-diastolic internal diameter: 5.1 ± 0.1 cm, LV end-systolic internal diameter: 3.3 ± 0.1 cm) (Figure 2). LV systolic function, as assessed by ejection fraction, was normal under control conditions (65 ± 1%) whereas LV diastolic function was impaired, as indicated by the low value of the early/late ratio, which appeared to be lower than the normal limit reported by Rokey et al 14 (Figure 2).

After 6 months of effective treatment with trandolapril, there was a reduction of LV mass index that was paralleled by reductions in interventricular septal and posterior wall thicknesses, whereas LV internal dimensions were unchanged (Figure 2). After 12 months of treatment, there was a further decrease of LV mass index associated with reduction of posterior wall and interventricular septal thicknesses and no change in LV enddiastolic (Figure 2) and end-systolic internal diameter (from 3.3 ± 0.1 to 3.3 ± 0.1 and to 3.2 ± 0.1 mm, at 6 and 12 months, respectively; difference not significant). No significant increases in LV mass index or interventricular septal and posterior wall thicknesses were found at the end of the washout period, compared with the 12-month values. Therefore, these parameters remained significantly lower than the corresponding initial values even after 1 month of withdrawal from therapy. The reversal of LV hypertrophy was accompanied by no change in LV systolic function (ejection fraction at 6 and 12 months and washout = $66 \pm 1\%$) despite calculated end-systolic stress, was significantly reduced during the effective treatment (control = 60 ± 3 ; 6 months = 55 ± 3 ; 12 months = 53 ± 3 dyne/cm², all p < 0.01 vs control) and returned to the basal value after the washout period (61 \pm 2 dyne/cm²; difference not significant). Conversely, there was an increase in LV diastolic function, evaluated by the early/late ratio, that increased significantly during treatment and remained higher than baseline at the washout control (Figure 2).

Effects on brachial artery compliance and forearm hemodynamics: During treatment with trandolapril, we found a statistically significant increase in brachial artery compliance (Figure 2) and diameter (from 0.54 ± 0.01 to 0.59 ± 0.01 and to 0.58 ± 0.01 cm at 6 and 12 months, respectively, both p < 0.01). After 1 month of withdrawal from the treatment, brachial artery compliance (Figure 2) and diameter (0.57 \pm 0.01 cm; p < 0.01) remained significantly higher than in control conditions, despite the systolic blood pressure having returned to basal values (Figure 1). Forearm vascular resistance, estimated by plethysmography, was significantly reduced by the treatment at 6 and 12 months, returned toward baseline after withdrawal

of trandolapril, but still remained significantly lower than in control conditions (Figure 1).

A significant inverse correlation was found between the changes in brachial artery compliance and those in LV mass index observed throughout the active treatment period (r = 0.519, p < 0.05) (Figure 3). Further, the changes in brachial artery compliance and those in LV wall thickness measured during the washout period were significantly and inversely correlated (r = 0.711, p < 0.01) (Figure 4).

DISCUSSION

The main finding of this study is the observation that long-term antihypertensive treatment with the ACE inhibitor trandolapril induces a uniform regression in cardiac and vascular structural changes. Our current observation that 1-year antihypertensive treatment with trandolapril induces a complete reversal of LV hypertrophy is not surprising,

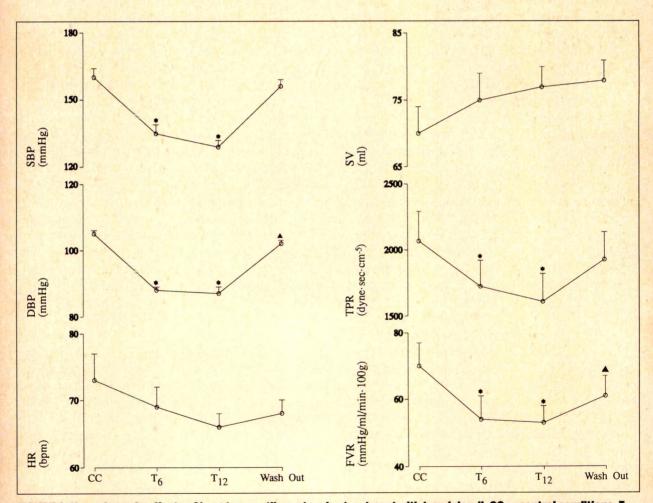


FIGURE 1. Hemodynamic effects of long-term antihypertensive treatment with trandolapril. CC = control conditions, T_6 and T_{12} = after 6 and 12 months of effective treatment with trandolapril; Wash out = after 1 month of withdrawal from therapy (n = 15; mean \pm SE). DBP = diastolic blood pressure; FVR = forearm vascular resistance; HR = heart rate; SBP = systolic blood pressure; SV = stroke volume; TPR = total peripheral resistance. * = p < 0.01 vs CC; Δ = p < 0.05 vs CC.

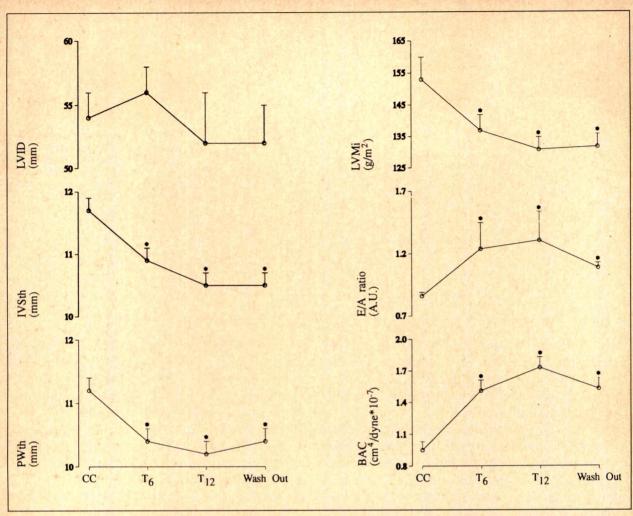


FIGURE 2. Effect of long-term antihypertensive treatment with transolapril (n = 15; mean \pm SE) on end-diastolic left ventricular internal dimension (LVID), end-diastolic interventricular septum thickness (IVSth), end-diastolic posterior wall thickness (PWth), left ventricular mass index (LVMI), ratio between early and late peak diastolic velocity (E/A), and brachial artery compliance (BAC). Other abbreviations and symbols as in Figure 1.

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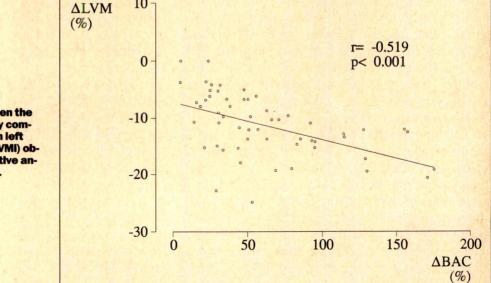


FIGURE 3. Relation between the changes in brachial artery compliance (BAC) and those in left ventricular mass index (LVMI) observed throughout the active antihypertensive treatment.

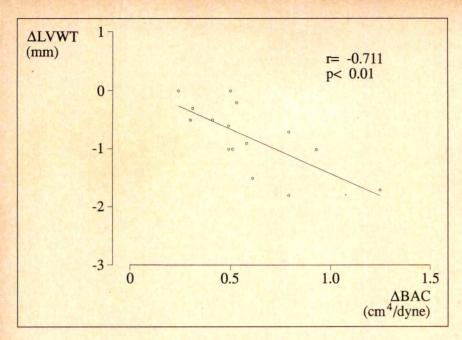


FIGURE 4. Relation between the changes in brachial artery compliance (BAC) and in left ventricular end-diastolic posterior wall thickness (LVWT) observed during the washout period.

since the ability of ACE inhibitors to reverse or prevent the progression of hypertension-induced LV hypertrophy more effectively than other therapies has been substantiated in both experimental^{16–18} and clinical¹⁹ studies.

There are many possible mechanisms through which ACE inhibitors may cause a more marked reduction of wall thickness and LV mass per unit (mm Hg) of blood pressure reduction, compared with other pharmacologic treatments. The reninangiotensin system seems to play an important direct and/or indirect role for the development of cardiac hypertrophy.²⁰ Therefore, it may be speculated that through the interference with this mechanism ACE inhibitors may prevent or revert LV hypertrophy more effectively than other drugs in the presence of a comparable antihypertensive effect. However, there are other antihypertensive drugs, such as β-adrenergic receptor blocking agents, which despite their ability to interfere with the renin-angiotensin system as well as with other trophic hormones, are less effective than ACE inhibitors in reverting LV hypertrophy.

Large artery compliance is a major determinant of LV hypertrophy in hypertension, 1,3 and ACE inhibitors have been shown to improve arterial compliance effectively. 2,6,7 This property may contribute to more marked reductions in afterload, even in the presence of similar reductions in blood pressure, and hence play a permissive role for the reversal of LV hypertrophy. Our finding of a significant inverse correlation between the reduction in LV mass and the corresponding increase in large artery compliance lends further support to this hypothesis. Further, an even stronger inverse

correlation was found in our study between the degree of reduction in LV posterior wall thickness and the increase in arterial distensibility evaluated after the washout period. This latter observation seems to suggest that ACE inhibitors are able to improve large artery compliance in hypertensive patients not only through the direct pharmacologic activity, as demonstrated in acute or short-term studies, ^{2,17,21} but also through the reversal of arterial structural changes. In fact, the data available on the pharmacokinetics of trandolapril²² rule out the possibility that the drug could still have been effective, even at the tissue level, after 1 month of washout.

On the other hand, the apparent discrepancy between our data and those obtained by Asmar et al⁷ with the administration of the ACE inhibitor perindopril may be accounted for by the observation that the patients included in that study showed in control condition a mean value of brachial artery compliance markedly higher than that measured in the patients included in our study as well as in a previous study performed in our laboratory with the administration of enalapril. More importantly, Asmar and colleagues⁷ suggested that the timeconstant for arterial structural changes in hypertensive patients may be different from that in LV hypertrophy. Thus, the longer follow-up period performed in our studies may also account for the discrepancy with the results obtained by Asmar and coworkers⁷ with a follow-up of 12 weeks. The hypothesis that the time course of reversal of arterial structural changes may be different from that of LV hypertrophy could be supported by the results obtained in several animal models of hypertension showing significant increases in collagen biosynthesis and total collagen content in large arteries. ^{23,24} In this regard, however, it has been reported that the improvement in large artery compliance induced by ACE inhibitors in rats with renovascular hypertension was associated with reduction of the thickness of aortic media without regression of the increase in the absolute amount of collagen. ²⁵ Therefore, the reversal of large artery structural changes seems to be mediated by a reversal of the hypertrophy of smooth muscle cells, as happens in the reversal of LV hypertrophy.

The correspondence of changes in LV and large artery walls may also be demonstrated by the improvement in cardiac diastolic function. In fact, although the improvement of early/late ratio during the treatment period may be explained also by the decrease in systemic blood pressure, the maintenance of an improved early/late ratio after 1 month washout period, when blood pressure was back to the basal value, suggests a direct effect of trandolapril on muscular tissue.

Our current observations may also concur to support the necessity for the chronic treatment of hypertension in humans. Several investigators^{20,26,27} have recently suggested that the pharmacologic therapy of hypertension may be discontinued in some patients after the achievement of certain therapeutic goals. In particular, regression of LV hypertrophy has been indicated as a significant end-point to consider the treatment satisfactory.²⁶ Our current data, however, seem to speak against this hypothesis. In our small experimental sample, despite regression of LV hypertrophy and improvement of large artery compliance with trandolapril, the interruption of the treatment was associated with a prompt increase in blood pressure. In fact, arterial blood pressure returned to baseline within the short time of 4 weeks. Therefore, the hemodynamic conditions that had produced structural damage were restored. These data suggest that to ensure a stable regression of the structural lesions that may predispose to the development of cardiovascular accidents, the therapeutic intervention should not be discontinued.

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Evaluation of the Antihypertensive Effect of Once-a-Day Trandolapril by 24-Hour Ambulatory Blood Pressure Monitoring

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The aim of this study was to evaluate the effects of trandolapril on 24-hour blood pressure in patients with mild-to-moderate essential hypertension. After a washout period of 4 weeks, 42 patients were randomized to receive 2 mg of trandolapril once daily and 20 to receive placebo in a double-blind fashion for 6 weeks. This was followed by a second washout period of 4 weeks. At the end of each period, clinic blood pressure was assessed at 24 hours after the last dose and 24-hour ambulatory blood pressure was measured noninvasively, taking blood pressure readings every 15 minutes during the day and every 20 minutes during the night. Two patients were dropped out before any blood pressure evaluation under treatment. Analysis of ambulatory blood pressure was performed in 48 patients who met the criteria for the minimal number of ambulatory blood pressure data (2 values per hour during the day and 1 value per hour in the night). In the trandolapril-treated group (n = 41) clinic systolic/diastolic blood pressures were 159.8 ± 2.0/ 102.4 \pm 0.8, 146.8 \pm 2.3/94.8 \pm 1.1, and 155.7 \pm 2.0/99.2 ± 0.7 mm Hg in the pretreatment, treatment, and post-treatment periods, respectively. The corresponding values for 24-hour mean blood pressure (n = 31) were 139.5 \pm 1.9/91.2 \pm 1.5, 131.0 \pm 2.0/84.3 \pm 1.2, and 139.7 \pm 1.8/90.9 \pm 1.1 mm Hg. The differences between the lower

treatment, versus the higher pre- and post-treatment, values were all statistically significant (p < 0.01). The trandolapril-induced blood pressure fall was similar during the day and night and statistically significant also during the last 4 hours of the 24-hour monitoring period ($-6.6 \pm$ 0.3 and -5.9 ± 0.2 mm Hg for systolic and diastolic blood pressure, respectively; p < 0.05). Trandolapril did not affect clinic heart rate but significantly lowered 24-hour heart rate values. In the placebo group the clinic (n = 19) and ambulatory (n = 17) blood pressure and heart rate values obtained at the end of the 3 periods were similar. Thus, at the dose of 2 mg once daily, trandolapril reduces blood pressure in mildto-moderate hypertensive patients. This antihypertensive effect is manifest throughout the 24 hours.

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randolapril is a newly developed angiotensin converting enzyme (ACE) inhibitor characterized by being a prodrug and having a relatively long half-life in plasma. ¹⁻⁴ Whether this makes the drug effective in reducing 24-hour blood pressure by once-a-day dosing has not been conclusively established, however. In the present study we have set out to examine this issue.

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METHODS

Study population: Our study was done on 62 outpatients with mild or moderate essential hypertension. The subjects (46 males and 16 females) had a mean age of 51.3 ± 1.5 years (range 29–67 years). They were recruited if their supine and standing diastolic blood pressure values, as assessed in the outpatient clinic, were ≥ 95 mm Hg at the end of the run-in period (see below). Other inclusion criteria were: (1) a body weight within the

normal limits for age, sex, and body surface; (2) no history or evidence of severe target organ damage (transient ischemic attacks, stroke, coronary heart disease, renal insufficiency, congestive heart failure, intermittent claudication, etc.); (3) no evidence of severe diseases in addition to hypertension; and (4) no history of hypersensitivity to ACE inhibitors. Each subject gave his or her consent to the study after explanation of its nature and purpose. After randomization to placebo or active treatment two patients were dropped out before any blood pressure evaluation under treatment. Therefore efficacy analyses were performed on 60 patients.

Study design: The study, which was a multicenter, randomized, double-blind, placebo-controlled, parallel-group design, had the following protocol. After an initial medical visit had shown a blood pressure elevation, the subjects were submitted to a run-in period of 4 weeks to allow washout from any previous treatment and to ensure diagnosis of the essential nature of their hypertension. The subjects were randomly assigned in a 2:1 ratio to trandolapril 2 mg once daily or to placebo for 6 weeks. The dose of trandolapril or placebo was administered at about 9 A.M. At the end of the 6 weeks, treatment was withdrawn and the patients were followed for another 4 weeks.

Clinical assessments: Before treatment, at the end of treatment, and after the treatment periods all patients had a physical examination, a 12-lead resting ECG, and biochemical, hematologic and urinary laboratory examinations. Adverse events were recorded at each visit upon enquiry from the investigator. At the end of each period, systolic and diastolic blood pressures were measured 3 times by sphygmomanometry (1st and 5th Korotkoff sounds, respectively), 10 minutes after assumption of the supine and 1 minute after assumption of the upright posture. The average of the last 2 readings in the supine position was taken as the reference clinic value. The concomitant heart rate values were assessed by the palpatory method over 1 minute. The measurements were obtained between 8 and 9 A.M., which for the treatment period corresponded to about 24 hours after dosing.

Ambulatory blood pressure monitoring: Ambulatory blood pressure and heart rate were monitored electronically (Spacelabs 5200; Spacelabs Inc., Redmond, Washington, USA). The monitoring started between 9 and 10 A.M., i.e., after completion of the clinic blood pressure measurements and, during the treatment period, immediately after the ingestion of the active drug or

	Placebo (n = 20)	$\frac{\text{Trandolapril}}{(n = 42)}$
Sex (male/female)	15/5	31/11
Age (years)	51.1 ± 1.7	51.4 ± 1.5
Weight (kg)	77.6 ± 2.8	73.4 ± 1.6
Height (cm)	169.0 ± 1.4	170.0 ± 1.2

placebo. The ambulatory blood pressure monitoring device was set to obtain one measurement every 15 minutes between 6 A.M. and 12 P.M. and one measurement every 20 minutes between 12 P.M. and 6 A.M. A recording was regarded as satisfactory if at least two readings per hour during the day and one reading per hour during the night (i.e., from midnight to 6 A.M.) were acceptable according to previously established criteria.5

Statistical methods: Ambulatory blood pressure data were analyzed as (1) 24-hour average systolic/diastolic blood pressure, mean arterial pressure, and heart rate; (2) daytime (6 A.M. to midnight) and night-time (midnight to 6 A.M.) average blood pressures and heart rates; and (3) hourly average systolic/diastolic blood pressure, mean arterial pressure, and heart rate. The analysis included the day-time and night-time mean arterial pressure and heart rate standard deviations of the mean values, which were taken as indices of blood pressure and heart rate variability.

Data from single subjects were averaged to obtain the means (± SE) of the group. A paired Student's t test was used to locate the differences between data obtained during treatment and before or after treatment. The statistical significance of the differences in the average hourly values was assessed by 2-way analysis of variance. A p < 0.05was taken as the minimum level of statistical significance throughout the study.

RESULTS

Demographic and medical history characteristics: Table I shows the demographic characteristics of the patients randomly treated with trandolapril or placebo. All data were comparable between the two groups.

Clinic blood pressure: As shown in Table II, in the group randomized to placebo, supine clinic systolic/diastolic blood pressures were not significantly different at the end of the run-in or baseline period, the treatment period, or the final treatment withdrawal period. In contrast, in the group randomized to trandolapril both systolic and diastolic

TABLE II Clinic Systolic/Diastolic Blood Pressure and Heart Rate Values at Run-in or Baseline, After Treatment with Placebo or Trandolapril, and After Washout

	Baseline	Treatment	After Treatment
Placebo (n = 19)			
SBP (mm Hg)	158.0 ± 3.1	151.7 ± 3.2	158.5 ± 1.9
DBP (mm Hg)	102.3 ± 1.1	101.1 ± 0.9	103.0 ± 1.0
HR (bpm)	73.9 ± 1.9	72.5 ± 1.8	72.8 ± 1.7
Trandolapril (n = 41)			
SBP (mm Hg)	159.8 ± 2.0	146.8 ± 2.3*	155.7 ± 2.0
DBP (mm Hg)	102.4 ± 0.8	94.8 ± 1.1*	99.2 ± 0.7
HR (bpm)	72.1 ± 1.3	72.0 ± 1.2	72.1 ± 0.8

Data are shown as means \pm SE. Asterisks refer to statistical significance of differences between baseline and treatment values (*p < 0.01). bpm = beats per minute; SBP, DBP = systolic, diastolic blood pressure; HR = heart

blood pressures decreased significantly in the treatment as compared to the baseline period, a significant increase being observed following treatment withdrawal. Heart rate was not significantly different throughout the study in either the placebo or the trandolapril-treated group. Similar results were obtained when considering blood pressure and heart rate values taken in the upright position (data not shown).

Ambulatory blood pressure: Twelve patients did not meet the criteria for the minimal number of ambulatory blood pressure data (see Methods). Thus, the analysis was carried out in 48 patients, 31 randomized to trandolapril and 17 to placebo. Figure 1 shows that in the placebo group, 24-hour average systolic/diastolic blood pressures and mean arterial pressure obtained at the end of the baseline period, the treatment period, and the post-treatment periods were superimposable. In contrast, in the trandolapril group all 24-hour average blood pressures were significantly less during the treatment period compared with the run-in and

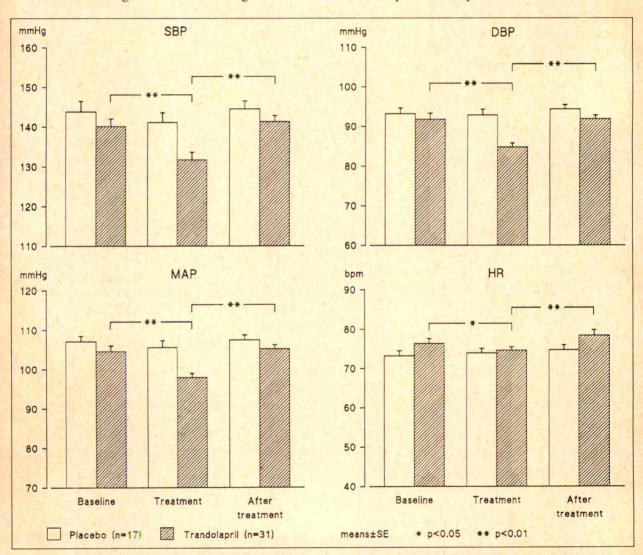


FIGURE 1. 24-hour systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) values at baseline, after 4 weeks of treatment with placebo ($open\ bars$) or trandolapril ($striped\ bars$) and after 4 weeks of washout. Data are shown as means \pm SE. Asterisks refer to the statistical significance of the differences between the 3 conditions.

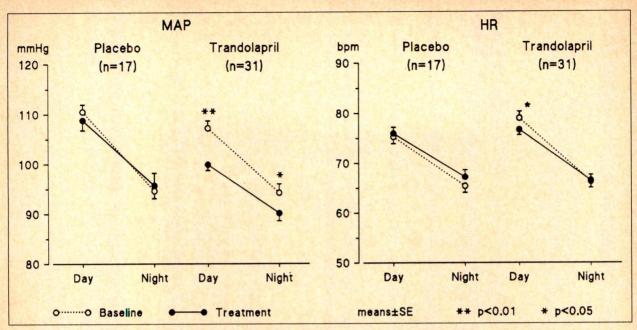


FIGURE 2. Day- and night-time mean arterial pressure (MAP) and heart rate (HR) values at baseline (open circles) and after treatment (solid circles) with placebo or trandolapril. Data are shown as means ± SE. Asterisks refer to the statistical significance of the differences between the 2 conditions.

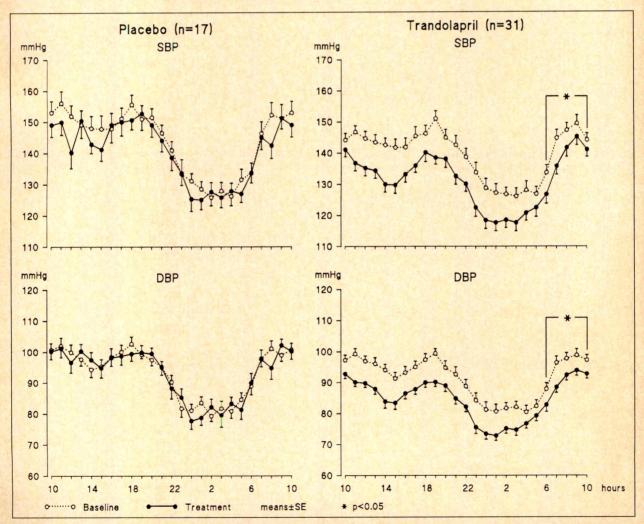


FIGURE 3. Hourly systolic blood pressure (SBP) and diastolic blood pressure (DBP) values at baseline (open circles) and after treatment (solid circles) with placebo or trandolapril. Data are shown as means \pm SE. Asterisks refer to the statistical significance of the differences in the last 4 hours between the 2 conditions.

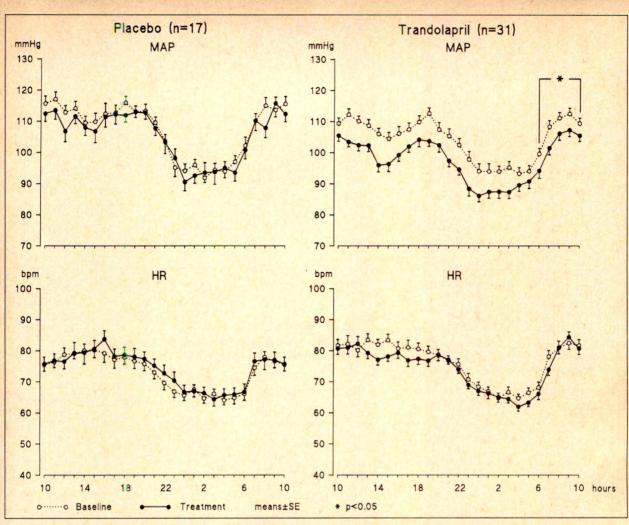


FIGURE 4. Hourly mean arterial pressure (MAP) and heart rate (HR) values at baseline (open circles) and after treatment (solid circles) with placebo or trandolapril. Data are shown as means \pm SE. For further explanations, see Figure 3.

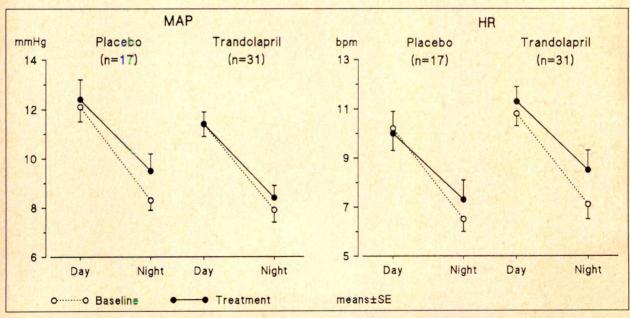


FIGURE 5. Day- and night-time variability of mean arterial pressure (MAP) and heart rate (HR) expressed as average standard deviations of the day and nighttime mean values. Data are shown as means \pm SE at baseline (open circles) and after treatment (solid circles) with placebo or trandolapril.

post-treatment periods. In contrast to placebo, trandolapril caused a significant reduction of both the elevated day-time and the reduced night-time blood pressure values (Figure 2). The trandolaprildependent reduction in blood pressure was evident during almost every hour during 24 hours and significant also for the last 4 hours of the 24-hour monitoring period (Figures 3 and 4). Average 24-hour, day-time, night-time, and hourly heart rates were not significantly affected by placebo and only slightly, although significantly, reduced by trandolapril (Figures 1-4). Blood pressure and heart rate variabilities were less during the night than during the day-time. In both instances placebo and trandolapril had no significant effect (Figure 5).

Safety: After randomization to placebo or trandolapril 2 patients dropped out: one patient had a stroke during placebo treatment while the second withdrew for reasons not related to the study treatment. The laboratory examinations and the ECG patterns were not significantly modified by treatment compared with the pretreatment values. In the trandolapril group, 3 patients complained of symptoms that were not considered to be related to the study drug (headache, gastric pain, and tinnitus). In the placebo group, one patient reported flushing and conjunctival hyperemia.

DISCUSSION

In our hypertensive subjects, once-a-day administration of trandolapril at the dose of 2 mg caused a significant reduction in 24-hour average blood pressure values compared with the pre- and post-treatment values. The reduction involved both systolic and diastolic blood pressures. It was evident with respect to the elevated day-time and the reduced night-time blood pressures, and it was manifest for the blood pressure values occurring in the last few hours of the 24-hour dosing interval. This permits the conclusion that at the dose employed, once-daily administration of trandolapril is therapeutically effective over 24 hours.

Several other data of our study deserve to be mentioned: (1) In our patients, trandolapril caused a significant although small reduction in 24-hour mean heart rate. This is not an invariable finding for antihypertensive treatment with ACE inhibitors. However, in some studies ACE inhibitors have been reported to potentiate vagal cardiac drive, which would account for the slight bradycardia we observed.⁶ (2) Trandolapril had no significant effect on either the elevated or the reduced blood pressure variability occurring during the day

and night, respectively. This may have clinical relevance, because in the setting of systemic hypertension, blood pressure variability is related to organ damage. 7,8 It should be emphasized, however, that noninvasive ambulatory blood pressure monitoring may not accurately measure blood pressure variability, because blood pressure readings obtained at 15 or 20 minute intervals miss a large number of blood pressure values and do not allow the resulting standard deviation to closely reflect the actual degree of the blood pressure oscillations.9 This may account for the fact that different effects on blood pressure variability have been reported in ambulatory blood pressure monitoring studies with several antihypertensive drugs. 10 It should also be emphasized that in a study in which blood pressure was measured beat-to-beat, trandolapril was shown to cause a reduction in blood pressure variability. 11 The findings of the present trial may thus underestimate the effect of the drug on this phenomenon.

Finally, in the patients randomized to placebo, clinic blood pressure fell whereas 24-hour mean blood pressure remained unchanged. Further, in the patients treated with trandolapril, treatment withdrawal was accompanied by an increase in clinic blood pressure, whereas no blood pressure effect occurred in the placebo group. Thus at variance from clinic blood pressure, 24-hour average blood pressure is devoid of any substantial placebo or time-related effect. ^{12,13} In other words, 24-hour blood pressure reflects the absence or presence of active treatment more adequately than clinic blood pressure. This emphasizes the advantages of using the former approach when investigating new antihypertensive drugs.

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The American Journal Cardiolog

A Symposium: ardiac Imaging and Patient **Management**

GUEST EDITOR:

Mario S. Verani, MD

Director, Nuclear Cardiology The Methodist Hospital Associate Professor of Medicine Department of Internal Medicine Baylor College of Medicine Houston, Texas

The American Journal of Cardiology.

A Symposium: Cardiac Imaging and Patient Management

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Director, Nuclear Cardiology
The Methodist Hospital
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Department of Internal Medicine
Baylor College of Medicine
Houston, Texas

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The American Journal

Introduction

Mario S. Verani, MD

his supplement to the American Journal of Cardiology contains the proceedings of a 1-day closed symposium, "Cardiac Imaging and Patient Management," held November 9, 1991, in Anaheim, California, in association with the 1991 Annual Meeting of the American Heart Association. This program brought together nationally recognized experts in the field of radionuclide cardiac imaging to discuss how to maximize the benefits of cardiac imaging in the clinical setting.

In my article, I provide an overview of thallium-201 (201Tl) single-photon emission computed tomography (SPECT) imaging and discuss the advantages of SPECT over planar scintigraphy for the detection of coronary artery disease. This review also examines pharmacologic stress imaging and discusses the benefits and risks of both dipyridamole and adenosine.

Robert Bonow discusses the assessment of myocardial viability with ²⁰¹Tl. He points out that viable myocardium may be present in some patients, even when none of the usual indicators (regional wall motion, systolic wall thickening, regional myocardial perfusion, and redistribution of thallium) so suggest. Clinicans would do well to look for this hibernating tissue, he suggests, either with positron emission tomography (PET) or with 201Tl SPECT imaging, performed either 8-72 hours after initial ²⁰¹Tl injection or after ²⁰¹Tl reinjection, to identify tissue that may be successfully revascularized.

George Beller explores the benefits of thallium scintigraphy in patients with severe left ventricular dysfunction. He notes that ²⁰¹Tl scintigraphy can identify viable asynergic segments when performed on patients with severe coronary artery disease who are in the resting state. Among his conclusions: There is a direct correlation between the extent of ²⁰¹Tl uptake in zones of severe regional myocardial asynergy and the magnitude of improvement in resting left ventricular ejection fraction after coronary bypass surgery.

In his article, Kenneth Brown provides an indepth look at cardiac prognosis with 201Tl scintigraphy. He explains that knowledge of a patient's coronary anatomy alone is often insufficient to predict who will benefit from revascularization. Clinicians also need to determine if the diseased vessels are supplying viable myocardium.

Finally, Frans Wackers evaluates the comparative benefits of SPECT scanning with thallium and the technetium-labeled agent sestamibi. His article reports the findings of several key comparative studies and describes several technical advances that have enhanced the diagnostic capability of ²⁰¹Tl imaging. In particular, the 2 agents are compared in terms of image quality and diagnostic value, as well as practical clinical usage.

A most striking consensus emerges from these articles. In spite of the introduction of newer agents, 201Tl SPECT remains an imaging modality of great value to nuclear cardiology because of its clinical benefits and the emergence of new imaging techniques, including reinjection and pharmaco-



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logic stress imaging. Moreover, improved thallium imaging is a powerful tool to assess jeopardized myocardium in symptomatic patients or in those with silent myocardial ischemia. Thus, it is anticipated that thallium will continue to play a significant role as the "gold standard" to which all new perfusion agents are compared.

We thank each of these distinguished contributors for sharing their perspectives on these issues. I would also like to acknowledge our communications company, Pragmaton, for their assistance with the organization of the symposium and for their attention to the editorial details of these articles.

Thallium-201 Single-Photon Emission Computed Tomography (SPECT) in the Assessment of Coronary Artery Disease

Mario S. Verani, MD

Of all currently available techniques, thallium-201 single-photon emission computed tomography (SPECT) is the most time-tested noninvasive method for the detection of coronary artery disease (CAD). Recent pooled data show an overall sensitivity of 90% and a specificity of 70% for thallium-201 SPECT. Of patients with singlevessel coronary disease, 83% are identified by **SPECT. Nearly all patients with double- and triple**vessel coronary disease (93% and 95%, respectively) are also identified. Thallium-201 SPECT imaging is also very effective in diagnosing CAD using pharmacologic stress testing. In certain patient populations (e.g., in sedentary patients or those using anti-ischemic medications), pharmacologic stress testing with dipyridamole or adenosine may be a logical alternative to exercise testing. Moreover, many patients have physical disabilities that preclude appropriate exercise testing. Intravenous adenosine is a very potent direct coronary vasodilator, with the advantage of an ultrashort half-life, which eliminates the need to administer an antagonist in the majority of patients. In addition, the dosage of adenosine can be adjusted during the infusion, if necessary.

The importance of thallium-201 SPECT during exercise or pharmacologic vasodilation transcends diagnosis, since it also plays an important role in the prognostic evaluation of patients with stable angina or postmyocardial infarction. Risk evaluation can be done with submaximal exercise electrocardiographic testing, but there is evidence that the addition of perfusion scintigraphy enhances the ability to predict future risk. In patients unable to exercise or to receive dipyridamole or adenosine stress, dobutamine has

recently emerged as yet another alternative. Although the reported experience is small with dobutamine thallium perfusion imaging, the test appears safe, well-tolerated, and has good sensitivity and specificity for CAD detection.

(Am J Cardiol 1992;70:3E-9E)

hallium-201 (201Tl) myocardial perfusion imaging has been widely used in the United States and abroad for the past 15 years. Recently, there has been renewed interest in this technique, despite predictions that new compounds labeled with technetium-99m would supplant ²⁰¹Tl. There are several reasons¹ for this renewed interest in ²⁰¹Tl: (1) improved myocardial images have resulted from the advent of scanning with single-photon emission computed tomography (SPECT); (2) recent improvements have been reported in quantification of the SPECT images; (3) the popularization of perfusion imaging in conjunction with pharmacologic "stress" of the cardiovascular system; and (4) the use of reinjection techniques to assess myocardial viability better. As a consequence, the number of myocardial perfusion imaging procedures continues to increase in many laboratories around the country.

This review summarizes recent findings on the diagnostic value of ²⁰¹Tl SPECT during exercise and of thallium scintigraphy in general during pharmacologic stress.

SENSITIVITY AND SPECIFICITY OF **THALLIUM-201 SPECT**

Data on 201Tl SPECT in conjunction with exercise from >1,000 patients have been pooled by Mahmarian et al (Table I).²⁻⁸ These data show an overall sensitivity of 90% for detection of coronary artery disease (CAD), with a range of 82–98%. Nearly all patients (99%) with prior myocardial infarction had abnormal SPECT images, but even in patients without prior myocardial infarction, the

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TABLE | Sensitivity and Specificity of Thallium-201 SPECT for Detecting Coronary Artery Disease

Study				Newpolev					
	% with MT	Overall	МІ	No MI	SVD	DVD	TVD	Specificity	Normalcy Rate
Tamaki ⁴ (n = 104)	39	98 (80/82)	100 (32/32)	96 (48/50)				91 (20/22)	
DePasquale ⁵ (n = 210)	25	95 (170/179)	100 (47/47)	92 (123/134)	91 (85/93)	99 (72/73)	100 (13/13)	74 (23/31)	
Iskandrian et al ⁶ (n = 461)	18	82 (224/272)	98 (49/50)	78 (174/222)	64 (45/70)	87 (93/107)	91 (86/95)	60 (35/58)	94 (123/131)
Maddahi ⁷ $ (n = 138) $	47	95 (87/92)	100 (43/43)	90 (44/49)	83 (15/18)	97 (32/33)	98 (40/41)	56 (10/18)	86 (24/28)
Mahmarian et al ² $(n = 360)$	33	87 (192/221)	99 (73/74)	79 (68/86)	84 (119/142)	91 (60/66)	100 (13/13)	87 (65/75)	
Van Train ⁸ (n = 318)	40	94 (185/196)	100 (78/78)	90 (106/118)	88 (56/64)	96 (69/72)	100 (60/60)	43 (15/35)	82 (62/76)
TOTAL	31	90 (938/1,042)	99† (322/324)	85 (563/659)	83 (320/387)	93‡ (326/351)	95‡ (212/222)	70 (168/239)	89 (209/235)

*Actual numbers are shown in parentheses.
†p = 0.0001 vs no MI; †p = 0.0001 vs SVD.
CAD = coronary artery disease; DVD = double-vessel disease; MI = myocardial infarction; SPECT = single-photon emission computed tomograhy; SVD = single-vessel disease; D = triple-vessel disease.

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sensitivity of ²⁰¹Tl SPECT for detecting CAD was quite high (average 85%).

The more extensive the CAD, the more likely it will be detected by SPECT. In the pooled data, 83% of patients with single-vessel disease and nearly all patients with double- (93%) and triple-(95%) vessel disease were identified by SPECT. The detection of all individual vessels with coronary stenosis is good, but not quite as high. Approximately 80% of all stenotic vessels are detected with SPECT, although detection of circumflex artery stenosis is lower.

Another important observation is that the sensitivity increases as the severity of coronary stenoses progresses from mild (<50% luminal narrowing) to moderate (50-70% luminal narrowing) to severe stenosis (>70% luminal narrowing). SPECT allows detection of nearly 90% of all stenoses with > 70% luminal narrowing.²

Analysis of pooled data² shows an overall specificity of 70% for detection of CAD with 201Tl SPECT during exercise, with a range on the order of 50-90%. Thus, in some laboratories, a poor specificity for SPECT may be the main limitation of the technique. The number of false-positive interpretations may be substantially decreased, however, by paying attention to pertinent history, such as the patient's gender and body habitus and the presence of anatomic factors leading to increased extracardiac attenuation. In our laboratory, quantification of myocardial perfusion images using an appropriate bank of normal perfusion data has enabled us to obtain a specificity of 90%.3 It has been previously emphasized that in many laboratories an abnormal perfusion scan is often used as a reason to perform coronary angiography. This results in a significant post-test selection bias, by which patients with normal perfusion scans typically do not undergo coronary angiograms, whereas those with an abnormal scan often go on to have an angiogram. Such a selection bias decreases the apparent specificity of the test. To overcome this problem, some investigators prefer to report "normalcy rate," i.e., the percentage of low-risk normal individuals with a normal scan. The normalcy rate is approximately 90% by ²⁰¹Tl SPECT.

QUANTIFICATION OF THALLIUM-201 SPECT IMAGES

In our laboratory, we use a polar-plot display method, which is a variation of the method originally described by Garcia et al⁹ with certain innovations that we have implemented.³ In summary, circumferential profiles are obtained on each of the short axis slices and the apical vertical long axis slices. Each of the slices is displayed concentrically on a "bull's-eye" format, where the center of the bull's-eye represents the apex of the left ventricle. The regions with normal myocardial activity are normalized to 100 and the abnormal regions scaled appropriately. Each patient's polar map is compared to a normal data bank, and the regions with decreased thallium activity (those with activities > 2.5 standard deviations below the normal mean) are color-coded to represent perfusion defects. Such a technique allows for computer quantification of the total left ventricular perfusion defect size (Figure 1), as well as the amount of reversibility at 4 hours, 24 hours, or after thallium reinjection.

EXERCISE THALLIUM-201 SPECT IN THE ASSESSMENT OF JEOPARDIZED MYOCARDIUM IN PATIENTS WITH CORONARY ARTERY DISEASE

Our group has recently evaluated the amount of myocardium jeopardized by stenoses of each of the 3 principal coronary arteries during exercise ²⁰¹Tl SPECT.¹⁰ In general, patients with left anterior descending artery stenosis have a larger myocardial perfusion defect size when compared with patients with right coronary artery or circumflex artery stenoses (Figure 2). In patients with left anterior descending artery stenosis, those in whom the stenosis is located in the proximal part of the artery usually have a larger myocardial perfusion defect than those with stenoses in the mid or distal location. Perhaps the most striking observation from this study, however, was the wide variation in myocardial perfusion defect sizes caused by stenosis of similar severity and in similar locations. The implications of these data are that the coronary angiograms alone cannot predict the amount of myocardium in jeopardy. Thus, the knowledge of the functional expression of the coronary stenosis (i.e., the extent, severity, and reversibility of the perfusion defects) complements the information obtained from the coronary angiograms.

A further observation from our study¹⁰ is that patients with more severe stenosis (>70% luminal diameter narrowing) in general have larger perfusion defects than those with narrowings in similar locations but of lesser severity (<70% stenosis).

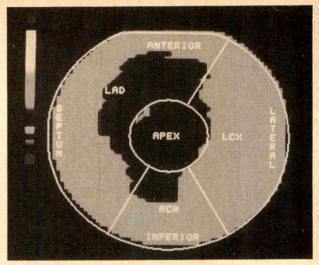
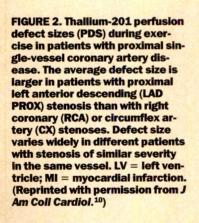
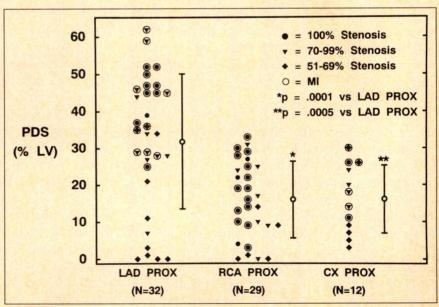


FIGURE 1. Buil's-eye polar map of the thallium-201 myocardial activity during exercise. The shaded area represents normally perfused myocardium and the inner area in black the perfusion defect, which amounted to 26% of the left ventricle in this patient with a proximal left anterior descending (LAD) stenosis. LCX = left circumflex; RCA = right coronary artery.

Here also, however, the coronary angiogram does not enable one to predict the extent or severity of the myocardial perfusion deficit. These observations are in keeping with the known difficulties in assessing the functional significance of angiographic coronary stenosis¹¹ and the variable contribution of coronary collaterals to the regional perfusion of different patients.

One of the potential criticisms of using exercise ²⁰¹Tl SPECT to assess the amount of jeopardized myocardium is that the perceived amount of jeopardized myocardium depends in large part on the intensity of the exercise test, ordinarily expressed by the maximal heart rate and double product





achieved. In other words, in patients with severe stenosis but with a poor exercise stress, the ²⁰¹Tl images may not reflect the true extent of their jeopardized myocardium. In fact, it is to be expected that the intensity of the exercise stress plays a significant role in the sensitivity of the test.⁶ As a corollary of this observation, patients with significant coronary stenoses who perform an exercise test of low intensity may have an entirely normal ²⁰¹Tl scan.

PHARMACOLOGIC MYOCARDIAL PERFUSION IMAGING

As discussed, the intensity of the exercise test is critical in order to obtain the highest possible yield from the ²⁰¹Tl SPECT images. We estimate that 20–30% of patients with suspected or documented CAD cannot perform a maximal exercise test. Of course, diverse physical disabilities may entirely preclude many other patients from performing exercise testing. For these patients, pharmacologic perfusion imaging is the logical approach.

Dipyridamole perfusion imaging: Dipyridamole is a potent, albeit indirect, coronary vasodilator that acts by blocking the cellular reuptake of adenosine, thereby increasing the blood and tissue concentrations of adenosine, which in turn produces maximal or near-maximal coronary vasodilation.¹² In normal coronary arteries, dipyridamole increases the flow to 3-4-fold times the baseline values (the so-called "coronary vascular reserve"). In arteries with stenosis of >50\% of the lumen diameter, the increase in flow will be proportionately less, however. In arteries with moderate stenosis (50–70% luminal narrowing), the coronary flow may still increase 2-3-fold above the resting values. On the other hand, in arteries with more severe stenosis (>70%), the flow increases much less or may not increase at all. This differential flow reserve in normal versus stenotic arteries provides the physiologic rationale for injecting imaging agents such as ²⁰¹Tl that are distributed according to the coronary blood flow. 13,14 When 201Tl is injected under conditions of coronary hyperemia, a differential distribution of ²⁰¹Tl is observed, with greater amounts of ²⁰¹Tl taken up by the normally perfused areas and lesser amounts by the abnormally perfused areas.

Leppo¹⁵ has pooled previously reported data on dipyridamole planar perfusion imaging and found an overall sensitivity of 90% and specificity of 70% for CAD detection. The sensitivity and specificity of ²⁰¹Tl imaging were similar during exercise or

dipyridamole stress testing in the patients who received both tests on different days.

In a study from our laboratory, Borges-Neto et al¹⁶ have demonstrated high sensitivity and specificity of ²⁰¹Tl SPECT imaging following high doses of oral dipyridamole. Thus far, no reports are available describing the corresponding values with intravenous dipyridamole; one would anticipate similarly high sensitivity and specificity.

In addition to its prominent role in the diagnosis of CAD, dipyridamole ²⁰¹Tl SPECT imaging has been found to be very useful in the cardiovascular risk stratification of patients undergoing peripheral vascular operations and in patients recovering from an acute myocardial infarction.

Recent evidence also suggests that pharmacologic vasodilation may be the ideal stress in patients suspected of having CAD and who also have a left bundle branch block. Patients with this conduction abnormality frequently show perfusion defects, usually involving the interventricular septum, that may closely mimic CAD. Interestingly, this is not a problem with dipyridamole imaging, and thus pharmacologic stress appears to be more specific than exercise scintigraphy in patients with left bundle branch block.

Although dipyridamole perfusion imaging is of proven value and has a good safety record, it has two potential drawbacks. First, dipyridamole may not elicit maximal coronary vasodilation in up to 20% of patients.¹⁷ Second, the elimination half-life of intravenous dipyridamole is several minutes, so that the effects of the drug as well as the side effects may persist for several minutes after ²⁰¹Tl administration. These side effects occur in approximately 50% of patients receiving dipyridamole¹¹ and in some cases are severe enough to require administration of the adenosine antagonist, aminophylline.

Adenosine perfusion imaging: Recently, adenosine perfusion imaging has been proposed as an alternative to dipyridamole perfusion imaging. 18 There are some distinct advantages of using adenosine as a coronary vasodilator. First, the ultrashort plasma half-life of adenosine (2–10 seconds) ensures that the effects of the drug will abate rapidly following termination of the test. Second, administration of adenosine may be titrated up or down, and the full effect of the new dose will be apparent in a matter of 1–2 minutes. Third, adenosine may elicit more consistent maximal coronary vasodilation than dipyridamole. 16 Our initial protocol with adenosine SPECT imaging used a stepwise titration of adenosine, beginning with a dose of 50

μg/kg/min and increasing the dose every minute to a maximum of 140 µg/kg/min. 18 In this protocol, ²⁰¹Tl was injected after 1 minute at the highest dose, which was then continued for an additional 2 minutes and then discontinued. This protocol proved to be very safe and yielded a high sensitivity and specificity for CAD detection. Subsequently, the protocol was simplified to a continuous infusion of 140 µg/kg/min for a total of 6 minutes, with thallium administered 3 minutes after the infusion started. This protocol has now been used in several thousand patients in the United States with an excellent safety record, high sensitivity and specificity, and excellent comparability with exercise ²⁰¹Tl SPECT imaging. 19,20 A recent report from our laboratory by Nishimura et al²¹ with computerized quantification of the SPECT images showed a sensitivity of 87% and specificity of 90% (Figure 3). Nguyen et al²² and Iskandrian et al²³ have also reported large series of patients receiving adeno-

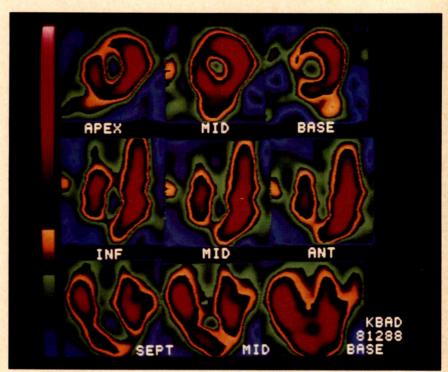


FIGURE 3. Thallium-201 singlephoton emission computed tomography (SPECT) images during adenosine infusion (top) and at redistribution (bottom) in a patient with left anterior descending stenosis. In each part, three representative slices are shown in the short axis (upper row), horizontal long axis (middle row), and vertical long axis (lower row). A defect (in orange color) involved the anterior (ANT) wall and apex in the adenosine images and filled-in in the redistribution images. INF = inferior; SEPT = septum. (Reprinted with permission from J Am Coll Cardiol.21)



sine ²⁰¹Tl SPECT, in whom the sensitivity was 90% and specificity 88%.

Side effects are common during administration of adenosine to patients.20-24 The most frequent side effects are facial flushing, chest pain, headaches, and dyspnea. Although frequent, these side effects disappear within 1-2 minutes of discontinuing the infusion and almost never require administration of aminophylline. The known negative dromotropic effect of adenosine in the atrioventricular node accounts for an occurrence of firstdegree atrioventricular block in approximately 10% of patients and a 3.6% frequency of second-degree atrioventricular block.24 Occasionally (<1%), thirddegree atrioventricular block occurs. Fortunately, as with the other side effects, atrioventricular block is transient and often disappears even when the infusion is continued. When necessary, the infusion may be terminated and the atrioventricular block will typically abate within several seconds.

Although most of the experience thus far reported with adenosine has been with 201Tl SPECT perfusion imaging, adenosine may also be used in combination with technetium-99m sestamibi (Verani et al, unpublished observations) or technetium-99m teboroxime imaging.25 Gupta et al26 have used adenosine stress in combination with positron emission tomography (PET) with excellent results. At the time of this writing, adenosine has yet to be approved by the Food and Drug Administration for use in conjunction with perfusion imaging, although adenosine is currently approved for emergency therapy of supraventricular tachycardia.

Dobutamine myocardial perfusion imaging: Although dipyridamole and adenosine represent important advances that have broadened the application of myocardial perfusion imaging in patients who could not previously undergo exercise stress testing, both dipyridamole and adenosine are contraindicated in patients with asthma or bronchospasm and must be used carefully in patients with low resting systolic blood pressures (<100 mm Hg). Further, neither dipyridamole nor adenosine should be used in patients who have recently used methylxanthine compounds (theophylline or caffeine) because these drugs antagonize the adenosine receptors in the cell membrane and thus may preclude the adenosine-induced vasodilation.

Mason et al²⁷ were the first to report dobutamine stress in combination with planar 201Tl perfusion scintigraphy. These authors reported a high sensitivity and specificity for this test. Subsequently, dobutamine was used in combination with ²⁰¹Tl scintigraphy by Zellner et al²⁸ and in combina-

tion with radionuclide angiography by Freeman et al.29 Recently, Pennell et al30 reported on the utility of dobutamine in conjunction with 201Tl SPECT (maximal dobutamine dose 20 µg/kg/min). Again, high sensitivity (97%) and specificity (80%) were reported.

Dobutamine stress imaging is performed in our laboratory using the following protocol. Dobutamine is infused intravenously at an increasing dose of 5, 10, 20, 30, and 40 µg/kg/min, with increases every 3 minutes. At the maximal tolerated dose, ²⁰¹Tl is injected and dobutamine maintained for an additional 2 minutes. The initial SPECT images are obtained immediately after stress, and the redistribution images are obtained 4 hours later. In a series of 144 patients recently studied in our laboratory, dobutamine stress was well tolerated, despite a high frequency of side effects. Sensitivity and specificity were 87% and 90%, respectively.³¹

Thus, dobutamine represents a third alternative for pharmacologic perfusion imaging in patients who are unable or unwilling to exercise. Together, these 3 drugs have considerably broadened the application of myocardial perfusion imaging.

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Assessing Viable Myocardium with Thallium-201

Robert O. Bonow, MD and Vasken Dilsizian, MD

Patients with chronic coronary artery disease and potentially reversible left ventricular dysfunction can often be successfully identified by one or more clinical indicators of myocardial viability, including regional wall motion, systolic wall thickening, regional myocardial perfusion as determined by perfusion tracers, and redistribution of thallium-201. In some patients, however, viable but "hibernating" myocardium will exist even when none of the above are evident. Myocardial viability in this situation can be detected with a high degree of accuracy by the demonstration of preserved metabolic activity by positron emission tomography (PET) scanning. Additionally, modifications of the standard exercise-redistribution thallium protocol may also produce accurate results. These modifications include late thallium-201 redistribution imaging, performed 8-72 hours following initial thallium injection, and thallium reinjection at rest after early (3-4 hours) or late (8-72 hours) redistribution imaging. These methods can identify viable myocardium in many thallium defects that appear to be irreversible on a standard 3-4 hour redistribution image. In addition, serial imaging after administration of thallium-201 at rest may also provide valuable insights into myocardial viability. These imaging modalities have important practical applications in the evaluation and management of patients with coronary artery disease and left ventricular dysfunction.

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n many patients with chronic coronary artery disease and left ventricular (LV) dysfunction, Limpaired LV performance represents a potentially reversible process (rather than irreversible fibrosis), a condition termed myocardial "hibernation." 1-3 Such patients may demonstrate substantial improvement, and even normalization, in LV function after successful revascularization. 1-6 In our experience, over one-third of patients with chronic LV dysfunction manifest a clinically meaningful increase in ejection fraction after myocardial revascularization. However, the identification of regions of the myocardium that are asynergic but "hibernating," with the potential for improved function after revascularization, is often a difficult clinical challenge, because these myocardial regions may mimic myocardial fibrosis, with absent or severely reduced wall motion and systolic wall thickening, and with moderate-tosevere reduction of perfusion at rest.

INDICATORS OF MYOCARDIAL VIABILITY

There are several clinically reliable indicators that may be used, alone or in combination, to identify viable myocardium in patients with chronic LV dysfunction. These include regional wall motion, regional systolic wall thickening, regional myocardial perfusion determined by perfusion tracers, and thallium-201 redistribution. However, viable myocardium can exist even in the absence of these indicators. This is particularly the case in the setting of myocardium hibernation, which, by definition, is associated with sufficient reduction in perfusion at rest to produce diminished or absent wall motion or wall thickening. 1-3 Such regions may also show apparent lack of thallium redistribution following standard exercise-stress tests and thus may appear persistently fixed on redistribution images, despite the presence of viable myocardium viability. Numerous studies indicate that "irreversible" thallium defects significantly overestimate the presence and severity of myocardial fibrosis.8-12

Gibson et al⁸ provided evidence for the existence of hibernating tissue by showing that roughly half of the irreversible thallium defects identified

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on exercise-redistribution thallium studies improve after revascularization (Figure 1). This finding has been confirmed in a number of subsequent reports. 9-12 Thus, standard exercise-redistribution thallium scintigraphy may not differentiate LV dysfunction arising from infarcted versus hibernating myocardium. For this reason, many investigators have shown great interest in the development of alternative methods, such as positron emission tomography (PET), to assess viable myocardium. PET can demonstrate the presence of preserved metabolic activity in viable myocardial regions with reduced blood flow. 13-21 Several recent studies, however, have shown that modifications of the standard exercise-redistribution thallium protocol may produce useful, clinically accurate results with thallium-201 single-photon emission computed tomography (SPECT). This review will focus on the use of these thallium methods to address the issue of myocardial viability.

LATE THALLIUM REDISTRIBUTION IMAGING

It is evident from several studies 11,22-24 that late redistribution imaging (performed 8-72 hours following the initial thallium injection at peak exercise) will demonstrate substantial redistribution in many defects that appear irreversible on a 3-4 hour redistribution image (Figure 2). For example, Kiat et al²³ evaluated 21 patients with thallium SPECT before and after myocardial revascularization with either coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. Thallium imaging was performed 15 minutes, 4 hours, and late (18–72 hours) after either exercise or pharmacologic stress. In these patients, 61% of apparently nonreversible defects at 4 hours showed reversal on late redistribution images. The 4-hour redistribution images did not accurately predict which segments with perfusion defects would improve after revascularization: 67 (85%) of the 79 segments showing redistribution at 4 hours as well as 88 (72%) of the 122 segments with fixed defects at 4 hours improved after revascularization (p = notsignificant). In contrast, the images taken at 18-72 hours effectively subcategorized the 4-hour nonreversible segments, enabling a more accurate prediction of improvement: 70 (95%) of the 74 segments showing late redistribution improved after intervention, whereas only 18 (37%) of the 48 late nonreversible segments improved (p < 0.0001). To optimize the assessment of the extent of viable myocardium by thallium-201, Kiat et al23 recommend that late redistribution imaging be performed when apparently nonreversible defects are encountered on 4-hour redistribution images.

In a separate study by the same investigators, Yang et al²⁴ assessed 118 patients using exercisestress thallium SPECT to determine the frequency of late redistribution. All patients had ≥2 segments with apparently nonreversible defects at 4-hour imaging and underwent late redistribution imaging between 18 and 72 hours. In 62 patients (53%), ≥ 1 of the defects that were fixed at the 4-hour redistribution imaging demonstrated late reversibility. In 41 patients (35%), ≥ 2 fixed defects were reversed at late imaging. Of 449 segments classified as reversible by performing both initial, 4-hour redistribution, and late redistribution imag-

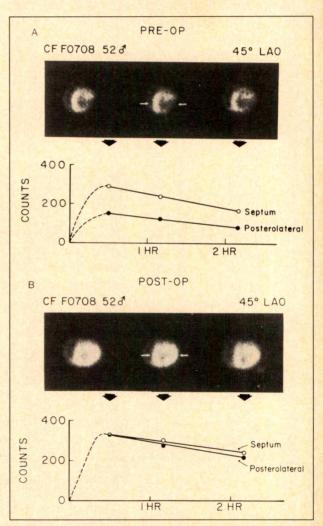


FIGURE 1. Evidence for viable myocardium despite an irreversible thallium defect in a patient studied by Gibson et al.8 A: Left anterior oblique (LAO) planar thallium-201 images are shown preoperatively (preop), indicating an irreversible defect in the posterolateral wall, which is confirmed by the count rates after exercise and at 1 hr and 2 hr. B: The postoperative (postop) study shows normalization of thallium activity in the posterolateral wall. The ejection fraction in this patient increased from 50% before operation to 65% after operation. Reprinted with permission of the American College of Cardiology.8

ing, 94% were also correctly identified by doing only initial and late imaging.²⁴

From these studies, it appears that late reversibility is frequent and may be evident in almost one half of patients with apparently irreversible defects on early (2–4 hour) redistribution. Late reversibility, like 4-hour reversibility, appears to indicate ischemic and threatened myocardium. Its implications in myocardial regions with asynergy are similar to those of early redistribution: viable myocardium exists and may possibly be salvaged through revascularization. If late reversible segments remain undetected, viable segments may be indistinguishable from fibrotic segments, possibly altering clinical management decisions.

Limitations of late redistribution imaging: The highly variable frequency of reversibility on late redistribution imaging that has been reported thus far in published series^{11,22–24} may arise from the small numbers of patients studied to date.

Discordant results may also be explained, at least in part, by differences in patient populations. Late redistribution is more likely to occur in patients with normal or hypokinetic wall motion than those with akinesia or dyskinesia and in patients without, compared to those with, previous Q wave infarction.^{11,22} Late redistribution in ischemic areas also may be related to the severity of stenosis in the involved coronary artery.^{22,23}

The mechanism for late redistribution may relate to the initial low uptake of thallium in regions with severe ischemia during exercise. Although subtle redistribution may occur in these regions, reduced thallium activity may continue to mimic the appearance of scar tissue at 4-hour imaging. The rate of thallium delivery during the post-exercise period could also be delayed in regions supplied by critically stenosed coronary arteries.

It is also possible that the redistribution of thallium depends in part on the subsequent serum

SHORT AXIS

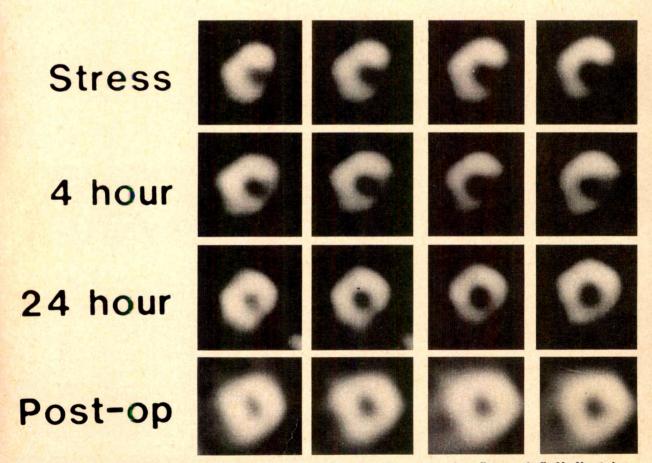


FIGURE 2. Effects of late redistribution imaging in a patient with 3-vessel coronary artery disease studied by Yang et al. 24 Short axis thallium-201 SPECT images obtained post-stress (top row) show a large lateral and inferior wall defect, which persists at 4 hr but reverses nearly completely at 24 hr. Repeat imaging post-stress after coronary artery bypass surgery (bottom row) shows normal thallium uptake. Reprinted with permission of the American College of Cardiology. 24

thallium concentration.²⁵ If serum thallium concentration decreases during the period between exercise and redistribution imaging, thallium delivery may be insufficient, resulting in persistent defects either at 4 hours or 24 hours, even though the underlying tissue is viable.²⁶ This suggests that some ischemic regions may never redistribute, even with late imaging, unless serum thallium levels are augmented.

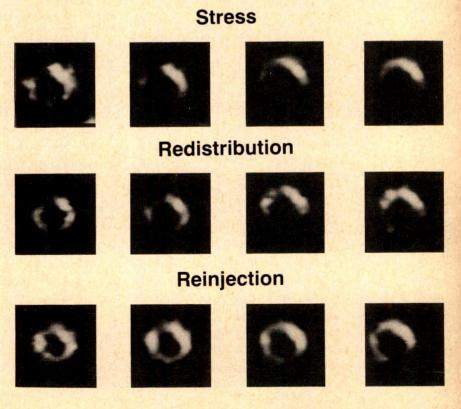
This concept is supported by data from several sources demonstrating that irreversible defects that persist even on late imaging continue to overestimate the presence and severity of myocardial fibrosis. Brunken et al²⁷ performed PET studies in patients undergoing late redistribution imaging and demonstrated that 53% of persistent thallium defects, even on late imaging, are metabolically active. Kiat et al²³ observed that 37% of irreversible defects on late imaging improve after revascularization. Finally, Kayden et al28 showed that 39% of irreversible defects at 24 hours manifest thallium uptake (that is, reversibility) when thallium is readministered at rest immediately after the 24-hour redistribution image. Thus, there are important limitations of late redistribution imaging. Late redistribution, when present, is highly predictive of viable myocardium; however, persistent defects on late imaging have very poor predictive accuracy.

THALLIUM REINJECTION IMAGING

The limitations of early and late redistribution imaging in identifying viable myocardium, when thallium is initially administered during exercise or pharmacologic stress, have led to the current interest in thallium reinjection techniques. In the past few years, several studies have reported the usefulness of thallium reinjection in determining myocardial viability. We studied 100 patients with coronary artery disease using exercise-stress thallium SPECT.²⁹ Standard redistribution images were obtained 3-4 hours following exercise, after which a second dose of thallium was administered. Of the 260 abnormal myocardial regions identified by stress imaging, 85 (33%) were irreversible on redistribution imaging, using a quantitative analysis of regional thallium activity. However, 42 (49%) of these apparently irreversible defects showed improved or normal thallium activity after thallium reinjection (Figure 3).29 These results have been confirmed by numerous other investigators. 12,28,30-33

Effects of myocardial revascularization: The results of thallium reinjection have a high predictive accuracy for identifying viable myocardium, as judged by the improvement in regional LV function after myocardial revascularization. In our original experience, ²⁹ 20 patients were restudied by radionuclide angiography and thallium scintigraphy 3–6 months after coronary angioplasty. Of 15 myocardial regions on the pre-angioplasty studies

FIGURE 3. Effects of thallium reinlection. Short axis thallium **SPECT images after exercise** (top) show extensive abnormalities in anterior, septal, inferior, and inferolateral perfusion. The septal defect partially reverses on 4 hr redistribution images (middle), but the other defects persist. All regions improve substantially after reinjection (bottom), with the exception only of the basal portion of the inferolateral wall, which remains irreversible. Reprinted with permission of W.B. Saunders Company.7.



with irreversible defects on redistribution images but enhanced thallium activity with reinjection, 13 (87%) had normal thallium uptake and improved regional wall motion after angioplasty. In contrast, all 8 regions with irreversible defects on reinjection imaging before angioplasty had abnormal thallium uptake and abnormal regional wall motion that persisted after angioplasty. Similar findings were reported by Ohtani et al¹² in a series of 23 patients, and more recently by Coleman et al³³ in a series of 18 patients.

Timing of imaging after reinjection: One issue regarding the thallium reinjection approach is the timing of imaging after reinjection. In theory, delaying imaging for several hours after reinjection would allow the reinjected dose to itself redistribute, thereby enhancing the detection of viable myocardium. However, this could create logistical difficulties by necessitating image acquisition very late on the day of testing or early the following day. We therefore determined whether imaging 24 hours after thallium reinjection provided additional information regarding tissue viability beyond that obtained by imaging shortly after reinjection.³⁴ We studied 50 patients, all of whom underwent a series of 4 thallium image acquisitions: stress, 3-4 hour redistribution, reinjection at 3-4 hours, and 24-hour redistribution. Of 127 initially abnormal myocardial regions on the stress images, 55 had persistent defects on redistribution imaging, of which 25 (45%) demonstrated improved thallium uptake after reinjection. At 24 hours, 23 of the 25 regions (92%) showing increased thallium uptake at reinjection showed no further improvement. Similarly, of the 30 regions determined to have irreversible defects after reinjection, 29 (97%) remained irreversible on 24-hour images. Quantitative analysis confirmed these findings. The mean normalized thallium activity in regions affected by reinjection increased from $57 \pm 13\%$ at redistribution to 70 ± 14% after reinjection, but did not change at 24 hours (71 \pm 14%). Similarly, among regions that had irreversible defects on both the early redistribution (51 \pm 22%) and reinjection $(54 \pm 20\%)$ studies, thallium activity was unaltered ($58 \pm 17\%$) on the 24-hour study. Only 4 regions, involving 3 patients, showed improved thallium activity at 24 hours as evidence of viability that was not apparent on either the early redistribution or the reinjection images. Thus, these data indicate that thallium reinjection after 3-4 hours of redistribution provides most of the clinically relevant information pertaining to myocardial viability in regions with apparently irreversible thallium defects on early redistribution studies.³⁴

However, the need for 3 sets of images (stress, redistribution, and reinjection) in a single day presents potential logistic difficulties. For this reason, alternative methods involving 2 imaging sessions have been explored. Kiat et al³⁵ investigated whether the early reinjection of thallium immediately following post-stress imaging would surmount this problem, by allowing the reinjected thallium dose to redistribute along with the initial dose injected during stress. A single 3-4 hour redistribution image might then incorporate both the redistribution and reinjection information. This would allow the acquisition of only 2, rather than 3, sets of images. Such an approach has obvious appeal, as it would simplify the logistics of patient flow in a busy nuclear cardiology laboratory. The results of this early reinjection protocol, however, demonstrated no real advantages.35 The frequency of late reversibility at 24-72 hours in myocardial regions with irreversible defects at 3-4 hours was similar with this early reinjection protocol to that observed with standard thallium-201 SPECT studies without reinjection. An early reinjection protocol, therefore, has not been proven to be an effective technique for assessing myocardial viability.

Thallium reinjection versus thallium redistribution: Because of the practical difficulties that arise in obtaining both redistribution and reinjection images in a large number of patients, many nuclear cardiology laboratories have adopted the practice of routinely replacing redistribution images with reinjection images at 3-4 hours. This approach, in which only 2 sets of images are acquired, simplifies imaging protocols and results in no change in patient flow compared to the pre-reinjection era. However, there is an important limitation of this approach that should be emphasized. It is true that this stress-reinjection protocol will provide accurate information regarding viability in most patients who would have had irreversible defects on standard redistribution images. However, in a number of patients with reversible defects on 3-4 hour redistribution images, reinjection causes an apparent "washout" of thallium in the ischemic zone^{29,36} which in some patients will result in the appearance of irreversible defects when only the stress and reinjection images are compared.³⁶ A reinjection image represents the superimposition of a resting perfusion image on a redistribution image. If flow is significantly reduced at rest in a vascular territory, which is likely to occur in patients with hibernating myocardium, the differential uptake of thallium after reinjection in the normally perfused zones relative to the ischemic zones may result in the reappearance of a perfusion defect in a region with a reversible defect on standard redistribution images. In support of this concept, patients who are likely to demonstrate this phenomenon are those with viable tissue that is totally dependent on collateral blood flow.³⁶ In our experience, roughly 25% of patients with LV dysfunction who have reversible thallium defects on 3-4 hour redistribution studies will manifest this apparent washout phenomenon.36 This has important implications, as the lack of a redistribution study in such patients will not only underestimate the presence and extent of viable tissue, but will also miss the important diagnostic and prognostic information stemming from evidence of inducible myocardial ischemia. The frequency of this finding is likely to vary considerably among laboratories depending on patient selection factors, but the possibility of a differential uptake effect should be considered if redistribution imaging is not performed.

In those patients in whom apparent thallium "washout" develops with reinjection because of the differential uptake of thallium, further redistribution of thallium does occur after reinjection, and this may be detected by a subsequent late redistribution image the next day.³⁶ That is, regions that manifest thallium redistribution between stress and 3-4 hours, but then have differential uptake with reinjection favoring the normal zones over the ischemic zones (causing the appearance of "washout"), will redistribute again over the next several hours after reinjection. In these patients, relative regional thallium activities on late redistribution studies are similar to those 3-4 hours.³⁶ These data indicate that there are 2 imaging protocols that will be effective in delineating both inducible myocardial ischemia and myocardial viability: stress-redistribution-reinjection imaging or stress-reinjection-late redistribution imaging. In either protocol, the third study is necessary only if irreversible defects are encountered on the second study.

Evidence that reinjection identifies viable myocardium: Several lines of evidence support the conclusion that the uptake of thallium after reinjection represents viable myocardium. First, as discussed previously, thallium reinjection results have a high positive and negative predictive accuracy regarding improvement in regional LV function several months after revascularization. 12,29,33 These revascularization results are comparable to the

predictive accuracies that have been reported in studies using metabolic PET imaging. 15,21

Second, in patients with chronic coronary artery disease and LV dysfunction who have been studied by both thallium reinjection and PET imaging with the positron emitter [18F]fluorodeoxyglucose (FDG), the vast majority of segments with thallium defects that were identified as viable by reinjection also had FDG uptake, 37-40 thus providing metabolic evidence for myocardial viability. In fact, the overall concordance between thallium reinjection and PET results has been excellent. These latter PET results also underscore the importance of using quantitative analysis of regional thallium activity, rather than mere qualitative reading of thallium images, for assessment of viability. In mild-to-moderate irreversible thallium defects (with thallium activity measuring >50% of activity in normal territories), >90% of regions manifest metabolic activity, independent of the results of thallium reinjection.^{37,41} It is in severe thallium defects (<50% of normal activity) that viability is in question. In severe thallium defects, thallium reinjection results are concordant with the results of PET imaging regarding viability versus nonviability in > 80% of myocardial regions. 37,41

Finally, comparison of regional thallium activity, before and after thallium reinjection, with indices of regional systolic wall thickening by magnetic resonance imaging⁴¹ indicates that the majority of regions identified as viable by thallium scintigraphy have preserved wall thickening, which is an accepted standard for viability. Patients in this study also underwent PET imaging. Importantly, in regions with absent wall thickening, in which the myocardium was either fibrotic or hibernating,42 there was an excellent concordance regarding the presence or absence of tissue viability between the results of thallium reinjection and assessment of metabolic activity by PET.41 These data indicate that thallium reinjection is a convenient, clinically accurate, and relatively inexpensive method with which to identify viable myocardium in patients with chronic coronary artery disease and LV dysfunction.

REST-REDISTRIBUTION THALLIUM IMAGING

The demonstration of exercise-induced ischemia in a patient with LV dysfunction has important prognostic implications that under most conditions identify that patient as a candidate for revascularization therapy. Thus, exercise-redistribution-reinjection thallium protocols are attractive, as they provide important information regarding both jeopardized myocardium and viable myocardium. However, in many patients the sole clinical issue to be addressed is the viability of one or more regions of dysfunctional LV myocardium, and not whether there is also inducible ischemia. In such patients, rest-redistribution thallium imaging is a practical approach that can yield accurate viability data. It is essential to obtain not only initial images (indicating regional perfusion) but also subsequent redistribution images. Although early thallium studies^{43–45} yielded mixed results regarding the predictive accuracy of rest-redistribution imaging, recent studies (published thus far principally as abstracts) indicate that a quantitative analysis of regional thallium activity in restredistribution studies predicts recovery of regional LV function⁴⁶ and compares favorably to the results of thallium exercise-reinjection imaging and metabolic PET imaging.47,48

CLINICAL IMPLICATIONS

The identification of viable myocardium has become an area of intense interest for several reasons. Among these is the rather unique potential of nuclear cardiology techniques to distinguish viable regions on the basis of perfusion, cell membrane integrity, and metabolic activity, thereby providing greater precision than can be achieved by assessment of regional anatomy or function. However, it must be emphasized that there are unresolved issues regarding the clinical applications of such techniques. 49 First, larger scale studies comparing PET and thallium-201, using reinjection techniques or resting injections, are required in patients undergoing revascularization to determine the relative efficacy of these two methods in identifying viable myocardium. There may be a number of patients in whom PET provides more accurate and complete data than can be accomplished using thallium imaging, but this number is not yet defined. Second, the use of dobutamine echocardiography to unmask contractile reserve in regions with resting dysfunction is an exciting approach, 50-52 and further studies are required to assess the efficacy of this approach versus that of the scintigraphic methods. Third, further information is also required to determine the efficacy of technetium-99m sestamibi SPECT imaging relative to these other modalities in assessing myocardial viability. 32,53,54 Finally, although roughly 85% of dysfunctional myocardial regions identified as viable by these various imaging techniques may improve after revascularization, it is unlikely that this will actually lead to clinical benefit in 85% of patients. Whether or not a clinically relevant change in ventricular performance occurs, and whether this translates into improved lifestyle and prognosis, will depend upon a number of factors, many of which are only poorly defined at present. The amount of dysfunctional but viable myocardium certainly is one such factor. At the current time, the identification of viable myocardium is not in and of itself an indication for revascularization. As in any other patient with coronary artery disease, this decision should be based on clinical presentation, coronary anatomy, left ventricular function, and evidence of inducible ischemia. The knowledge that a large region of left ventricular myocardium is viable rather than irreversibly damaged will aid in this decision-making process, but it should not be the primary indication for revascularization.

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Myocardial Thallium-201 Scintigraphy for Assessment of Viability in Patients with Severe Left Ventricular Dysfunction

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Many patients with ischemic heart disease and depressed left ventricular (LV) function have asynergic zones with sustained microcirculatory perfusion and myocardial metabolic activity that exhibit improved systolic function after coronary revascularization. The 2 predominant noninvasive techniques used to determine myocardial viability in patients with severely depressed LV function are thallium-201 (201TI) scintigraphy and positron emission tomography (PET). Myocardial extraction of 201TI is unaltered under experimental conditions of myocardial stunning or shortterm hibernation (characterized by decreased flow and ischemic dysfunction). Akinetic or dyskinetic LV wall segments can exhibit normal or near normal 201TI uptake as long as some residual flow is present. 201Tl scintigraphy can identify viable asynergic segments when performed on patients with severe coronary artery disease who are in the resting state. Many of these patients have initial resting defects that demonstrate delayed redistribution, or mild persistent defects that show improved perfusion and function after revascularization. There is a direct correlation between the extent of 201TI uptake in zones of severe regional myocardial asynergy and the magnitude of improvement in resting LV ejection fraction after coronary bypass surgery. Rest 201TI scintigraphy may help in the selection of patients with coronary artery disease and severely depressed LV function who would benefit the most from revascularization.

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Tany patients with ischemic heart disease and depressed left ventricular (LV) function have asynergic zones with sustained metabolic activity that exhibit improved systolic function after coronary revascularization. 1-3 In patients with chronic, stable, coronary artery disease, these resting asynergic segments have been designated as "hibernating." An accurate, noninvasive determination of myocardial viability in such regions of abnormal function is critically important to the practicing physician, because it can assist in clinical decision making and help to identify patients who will benefit from revascularization, as opposed to patients with LV dysfunction due to irreversible myocardial cellular injury, who are not expected to demonstrate improved regional myocardial perfusion and function after coronary bypass surgery or angioplasty. Noninvasive techniques that measure global and regional function (e.g., echocardiography and radionuclide angiography) are not as useful in determining myocardial viability in hibernating myocardial zones as are techniques that assess preserved cellular cationic transport (Ca²⁺, K⁺, Na⁺) or metabolism.

Thallium-201 (²⁰¹Tl) scintigraphy⁵⁻⁹ and positron emission tomography (PET) with simultaneous evaluation of flow and [18F]fluorodeoxyglucose (FDG) metabolism, respectively, 10-12 are currently the most widely used noninvasive techniques for the determination of myocardial viability in patients with severely depressed LV function. 201Tl scintigraphy, performed solely in the resting state, may be the most clinically useful approach for distinguishing between viable and nonviable myocardial regions in patients with chronic ischemic heart disease and depressed LV function and in those who exhibit clinical manifestations of congestive heart failure. 13-18

MECHANISM AND DETERMINANTS OF MYOCARDIAL THALLIUM-201 UPTAKE

²⁰¹Tl is a monovalent cation that is predominantly transported by active processes utilizing the

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sodium potassium adenosine triphosphatase (Na+,K+-ATPase) system. After intravenous injection, the uptake of ²⁰¹Tl by myocardial tissue is proportional to regional blood flow and the ²⁰¹Tl "extraction fraction." (The first-pass extraction fraction is the percentage of a ²⁰¹Tl dose entering the coronary circulation that is taken up by myocardial cells on first transit.) Under normal conditions, the extraction fraction is in the range of 85%. If ²⁰¹Tl imaging is to be a useful technique for determination of myocardial viability, it must be shown that it is normally extracted when there is hibernation or postischemic myocardial stunning.

In previous studies, Moore et al¹⁹ and Sinusas et al²⁰ sought to determine the transport kinetics of ²⁰¹Tl under experimental conditions of myocardial stunning and short-term hibernation.

In an experimental canine model of stunned myocardium, Moore et al¹⁹ showed that ²⁰¹Tl uptake and washout kinetics were unaltered. This was characterized by severe systolic dysfunction observed after repetitive, brief periods of coronary occlusion. To produce myocardial stunning, openchest dogs with a critical left anterior descending (LAD) coronary stenosis underwent 10 5-minute periods of total LAD occlusion, each interspersed with 10 minutes of reflow through the critical stenosis. Figure 1 (top) shows the serial changes in systolic thickening in the LAD zone during the course of this experiment, compared with measurements of systolic thickening in a comparable group of control dogs that had a critical LAD stenosis but did not undergo the stunning procedure. In the stunned dogs, systolic thickening in the LAD zone fell to $0.4 \pm 2.4\%$ at the 10th 5-minute period of LAD occlusion, compared with $32 \pm 2\%$ thickening in control dogs. Despite this virtual akinesis in the LAD zone, the first-pass extraction fraction of ²⁰¹Tl was 0.78, a value identical to that measured in control animals (Figure 1, bottom). The mean washout rate for both stunned and control dogs showed no significant differences in either the fast or slow components of the washout curve. Thus, these data indicate that myocardial stunning produces severe, postischemic LV dysfunction and is associated with normal uptake and washout transport kinetics of ²⁰¹Tl administered via the intracoronary route.

In another canine model of stunning characterized by 15 minutes of total LAD occlusion followed by reperfusion, Sinusas et al²⁰ confirmed the results of Moore et al.¹⁹ In the model used by Sinusas et al, ²⁰¹Tl uptake was unaltered by stunning. In addition, Sinusas and colleagues also examined ²⁰¹Tl

uptake in a chronic low-flow canine model of short-term hibernation. In this investigation, coronary blood flow was reduced by 38% and distal coronary pressure was reduced by 45%. This produced severe systolic dysfunction and was also associated with preserved ²⁰¹Tl uptake. Several other studies, however, have indicated that necrotic myocardial cells cannot sequester ²⁰¹Tl. ^{21–24}

Taken together, these experimental data suggest that intracellular extraction of ²⁰¹Tl is not impeded unless there is a reduction in blood flow preventing delivery of the radionuclide to the cell or there is irreversible sarcolemmal membrane injury that prevents ²⁰¹Tl extraction. The experimental literature indicates that hibernation states alone, and myocardial stunning after brief periods of

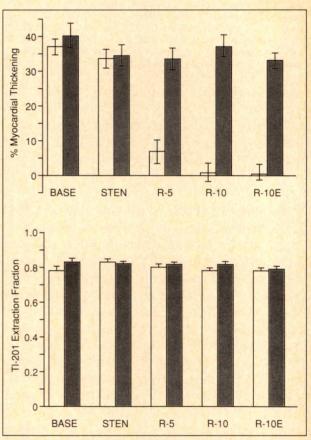


FIGURE 1. Top: Serial changes in percentage of myocardial thickening in stunned (open bars) and control (shaded bars) dogs at baseline (BASE), after creation of a critical left anterior descending coronary artery (LAD) stenosis (STEN), after the 5th 5-minute LAD occlusion and reperfusion (R-5), after the 10th 5-minute LAD occlusion and reperfusion (R-10), and 40 minutes after the 10th occlusion (R-10E). Stunning was produced by 10 5-minute LAD occlusions, each interspersed by 10 minutes of reflow. Control dogs underwent the LAD stenosis only and were serially assessed. Bottom: Bar graph showing first-pass thallium-201 (201TI) extraction fractions in stunned (open bars) and control (shaded bars) dogs at time defined in top graph. Note no alteration in 201Tl extraction at R-10 and R-10E despite severe reduction in systolic thickening. (Reprinted with permission from Circulation.19)

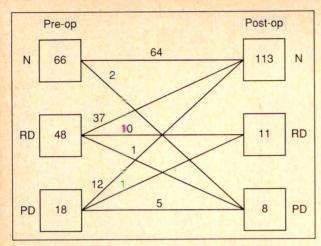


FIGURE 2. Comparison of preoperative (Pre-op; left) and postoperative (Post-op; right) segmental thallium-201 (201TI) uptake in 22 patients with severe stable or unstable angina undergoing rest 201Tl scintigraphy. Number of normal (N) segments, redistribution segments (RD), and segments with persistent defects (PD) are shown in boxes. Improvement in initial 201TI uptake after bypass surgery is reflected by number of segments improving one grade. (Reprinted with permission from Circulation. 13)

transient coronary occlusion, do not inhibit 201Tl extraction as long as there is some preservation of blood flow and no associated necrosis. Akinetic or dyskinetic segments can exhibit normal or nearnormal 201Tl uptake as long as some residual flow is present.

THALLIUM-201 REDISTRIBUTION AND VIABILITY

Following the first-pass myocardial uptake phase after intravenous tracer administration, there is a constant exchange of 201Tl between the myocardium and the extracellular compartments. 201Tl is continuously being washed out from normally perfused myocardium and replaced by 201Tl with residual activity recirculating in the blood pool. This process of continuous kinetic exchange forms the basis of ²⁰¹Tl redistribution. The term redistribution implies delayed defect resolution and is seen when ²⁰¹Tl is administered during transient underperfusion of the myocardium or when there is a chronic reduction in myocardial blood flow, which is referred to as rest redistribution. 25 Defects demonstrating delayed redistribution are further subclassified as showing either total or partial redistribution.6 Partial redistribution is often seen when there is a mixture of necrosis and reversibly ischemic myocardium.

Defects that demonstrate a persistent diminution of 201Tl uptake over time have also been subdivided as "severe" or "mild" persistent defects. Persistent defects observed on serial imaging, after exercise, pharmacologic stress, or serially in the resting state were originally thought to represent solely infarction or scar. Several studies have shown, however, that approximately 30% of persistent ²⁰¹Tl defects show improved ²⁰¹Tl uptake after revascularization. 6,26 This suggests that these persistent defects had some residual viable myocardium present. Persistent defects that tend to normalize or show enhanced ²⁰¹Tl uptake after revascularization are usually of the mild category, with no more than a 25-50% reduction in ²⁰¹Tl uptake. Most severe persistent defects demonstrating a ≥50% reduction in ²⁰¹Tl counts compared with a normal region rarely show improved 201Tl uptake after revascularization.6

REST THALLIUM-201 CLINICAL IMAGING STUDIES FOR ASSESSMENT OF VIABILITY

²⁰¹Tl scintigraphy, performed entirely in the resting state, has been used to evaluate resting myocardial blood flow in patients with severe, chronic, stable angina and in patients with unstable angina. Berger et al¹³ reported that 73% of ²⁰¹Tl defects in a group of patients with severe stable or unstable angina showed some delayed redistribution (as measured by quantitative planar techniques). In that study, 37 of 48 segments that showed preoperative rest ²⁰¹Tl redistribution exhibited significant improvement in ²⁰¹Tl uptake after coronary bypass surgery (Figure 2). Many of the mild persistent defects seen preoperatively showed improved ²⁰¹Tl uptake after revascularization. In contrast, few severe persistent defects (>50% reduction in uptake) showed an improvement in postoperative ²⁰¹Tl uptake.

Gewirtz et al14 and Hakki et al15 have also reported that in patients with coronary artery disease, a substantial number of severely asynergic segments exhibit preserved 201Tl uptake or rest redistribution. However, in these studies there were no postoperative assessments of perfusion or function.

More recently, Ragosta et al²⁷ performed preand postoperative rest ²⁰¹Tl scintigraphy and rest radionuclide angiography on 21 patients who had coronary artery disease and ejection fractions of <35%. Most patients had clinical signs or symptoms of congestive heart failure when they entered the study. The majority of patients had asynergic myocardial segments showing total to partial preservation of ²⁰¹Tl uptake after resting injection preoperatively (i.e., normal uptake, an initial resting defect with delayed partial or total redistribution, or a mild persistent defect with < 50% reduction in ²⁰¹Tl activity).

There was a direct correlation between the

extent of residual ²⁰¹Tl uptake on the delayed preoperative scan and the rise in global ejection fraction after surgery. Interestingly, Ragosta et al²⁷ found that asynergic segments corresponding to mild persistent ²⁰¹Tl defects had the same probability for improved function after revascularization as did segments corresponding to normal initial ²⁰¹Tl uptake or defects exhibiting delayed redistribution.

Bonow et al⁹ have also shed light on the issue of viability and mild persistent ²⁰¹Tl defects. In their study employing SPECT imaging, most mild (60-84% of normal) or moderate (50–59% of normal) persistent defects showed evidence of viability, as assessed by [18F]FDG uptake on PET scans. Severe defects (<50% of normal activity) showed less evidence of viability on PET scans. Thus, the actual level of 201Tl activity in persistent defects on delayed images can, by itself, be used as an index to predict the presence of viable myocardium. Mild reduction in ²⁰¹Tl uptake on serial images, without the necessity of demonstrating redistribution, indicates preserved viability and, therefore, a high probability of enhanced perfusion and function after revascularization. Table I provides a summary of proposed criteria for designating viability by quantitative rest ²⁰¹Tl scintigraphy.

REST THALLIUM-201 SCINTIGRAPHY IN CLINICAL DECISION MAKING

The experimental and clinical data cited previously indicate that preoperative imaging with resting injection of ²⁰¹Tl can help to identify patients with chronic ischemic heart disease and depressed LV function who would most likely show an improvement in heart function after bypass surgery. Although patients with multivessel disease and a severe reduction in LV function show more favorable outcomes with bypass surgery than they do with medical therapy, the survival rate for bypass surgery patients over a 5-10-year period is not optimal.²⁸ This may be due to the fact that some patients with severe depression of LV function underwent revascularization of irreversibly injured and nonviable myocardium. Despite technically successful revascularization, these patients may continue to exhibit progressive LV failure with cardiac dilation and they may finally succumb to a fatal ventricular arrhythmia. Patients who show no improvement in myocardial function after bypass surgery will most likely show a markedly reduced ²⁰¹Tl uptake before surgery, as well as myocardial thinning on echocardiography or magnetic resonance imaging.

Patients with ejection fractions as low as 10-

TABLE I Proposed Criteria for Designating Viability by Quantitative Rest Thallium-201 Scintigraphy

Assessment	Criteria					
Normal viability	Normal initial thallium-201 (201Tl) uptake and washout. An initial defect of any magnitude with delayed total redistribution. An initial defect with partial redistribution in which 201Tl activity on final image is < 50% reduced compared with normal. A persistent defect on serial images in which 201Tl activity is 20–50% reduced compared with normal.					
Mild reduction in viability						
Severe reduction in viability	A severe, persistent defect on serial images in which ²⁰¹ Tl activity is > 50% reduced compared with normal					

15% may have a considerable amount of hibernating myocardium, with residual viable myocardium in the distribution of severely stenosed vessels. Physicians would be less reluctant to advise surgery for these types of patients if they could be assured that the akinetic zones observed on ventriculography had a high probability of showing improvement in function after surgery. Demonstration of preserved ²⁰¹Tl uptake, albeit reduced, would provide the evidence that is necessary to predict a favorable outcome with revascularization. Further clinical trials are warranted to determine prospectively whether patients who have a markedly reduced ejection fraction (and who show residual viability by ²⁰¹Tl criteria) do indeed experience improved survival with revascularization when compared with patients who have a similar reduction in global LV function, but whose asynergy is due primarily to irreversible myocardial injury (as reflected by severe reduction in 201Tl activity on delayed rest imaging).

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Prognostic Value of Thallium-201 Myocardial Perfusion Imaging in Three Primary Patient Populations

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Knowledge of a patient's coronary anatomy alone is often insufficient to predict who will benefit from revascularization. Risk of cardiac events is related more to the presence of viable myocardium supplied by coronary arteries that are hemodynamically significant. Myocardial perfusion imaging with thallium-201 has been shown to reveal the presence and extent of jeopardized viable myocardium. In addition, thallium-201 imaging can demonstrate exercise-induced left ventricular dysfunction, manifested by increased lung uptake. Therefore, it is not surprising that thallium-201 myocardial imaging has important prognostic value in a wide spectrum of patients with coronary artery disease. The use of thallium-201 to predict cardiac events in patients with known or suspected coronary artery disease, in patients following myocardial infarction, and in patients undergoing noncardiac surgery is reviewed.

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anagement decisions regarding patients with coronary artery disease have traditionally been based on a combination of clinical findings, cardiac catheterization data, and left ventricular function. Astute clinicians have long recognized that coronary anatomy alone does not provide all the information necessary for effective management decisions. During the past decade, thallium-201 (201Tl) perfusion imaging has been consistently shown to have significant prognostic value in various patient groups with coronary artery disease.1 This prognostic value has been demonstrated in 3 primary patient populations: (1) patients with known or suspected coronary artery disease; (2) patients with a recent myocardial infarction; and (3) patients undergoing noncardiac surgery.

THALLIUM-201 MYOCARDIAL PERFUSION IMAGING

Myocardial uptake of ²⁰¹Tl occurs by both passive diffusion and active mechanisms involving the sodium-potassium (Na+,K+-ATPase) pump.1 Importantly, myocardial ²⁰¹Tl extraction is not diminished in reversibly damaged myocytes; only irreversibly damaged myocytes demonstrate depressed ²⁰¹Tl uptake. Most significantly, the relation between thallium uptake and myocardial blood flow is relatively linear.² Therefore, regional differences in myocardial blood flow caused by coronary artery disease will be manifested by regional differences in 201Tl uptake, resulting in "defects" seen in myocardial thallium images. Transient defects (i.e., defects that show enhanced uptake over time) reflect hypoperfused but viable myocardium. Thus, ²⁰¹Tl uptake reflects both relative myocardial blood flow and viability.

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BASIS FOR THE PROGNOSTIC VALUE OF THALLIUM-201

Transient thallium-201 defects: Transient defects define the presence of jeopardized or hypo-

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perfused viable myocardium and are the most consistent predictors of future cardiac events.1 Although the presence of angiographic coronary disease establishes an increased risk of cardiac events, risk seems to be more directly related to the presence of a hemodynamically significant lesion in a vessel that supplies viable myocardium. Angiographic anatomic assessment of coronary artery disease often does not accurately reflect the hemodynamic impact on coronary blood flow. In contrast, 201Tl uptake reflects relative perfusion, independent of anatomic considerations.

A diseased coronary artery that supplies an area of prior infarction is not likely to cause the same risk of future cardiac events as the same artery supplying viable myocardium. This may explain the consistent lack of predictive value of fixed 201Tl defects because such defects generally reflect prior infarction or scar.1

Thallium-201 lung uptake: Increased 201Tl lung uptake on exercise myocardial perfusion studies has also been shown to have important prognostic value.1 Increased lung uptake has been shown to be associated with left ventricular dysfunction and severe, extensive coronary disease.3,4 Although the pathogenesis is not completely understood, increased lung uptake has been positively correlated with stress-induced increases in pulmonary capillary wedge pressure and pulmonary transit time,5 and negatively related to changes in cardiac output.6 These observations suggest that uptake of ²⁰¹Tl in the lungs is dependent on hydrostatic pressure in the pulmonary capillary bed as well as factors that influence pulmonary tissue contact time and thus extraction efficiency.1 The result is an indirect index of diffuse ischemia and/or left ventricular dysfunction that, not surprisingly, has prognostic value.

PROGNOSTIC VALUE OF THALLIUM-201 IMAGING

Patients with known or suspected coronary artery disease: Brown and colleagues7 were the first to demonstrate a direct relation between the presence or extent of jeopardized viable myocardium, as assessed by 201Tl imaging, and the risk of future cardiac events. In 100 patients with no known prior myocardial infarction who were evaluated on the basis of chest pain, the predictive value of 201Tl imaging was compared with clinical, exercise electrocardiographic, and angiographic data using multivariate logistic regression analysis (Table I).7 The most accurate predictor of future cardiac events (cardiac death or myocardial infarc-

tion) was the number of myocardial segments with transient 201Tl defects. A number of subsequent studies have confirmed this observation (Table I). Consistently, the presence, extent, and severity of transient defects have been found to predict future cardiac events in patients presenting with known or suspected coronary artery disease.2,7-19

Other studies have found that increased lung uptake of 201Tl is also a significant predictor of future cardiac events. 14,15 Gill et al14 found that increased lung uptake of 201Tl was the best predictor of cardiac events in a series of patients with suspected coronary artery disease undergoing exercise ²⁰¹Tl imaging. Kaul et al¹⁵ also found increased ²⁰¹Tl lung uptake to be the best predictor of cardiac events, although both the presence of defects with redistribution and the number of angiographically diseased vessels had significant multivariate predictive value when lung activity was not considered.

Several recent articles¹⁷⁻¹⁹ have reported that ²⁰¹Tl imaging performed in conjunction with dipyridamole-induced coronary hyperemia also has important prognostic value. Using intravenous dipyridamole infusion in conjunction with thallium scintigraphy, Younis et al¹⁷ studied 107 asymptomatic patients with coronary artery disease. Of the 107 patients studied, 36 had normal thallium scans and 71 had abnormal scans. Patients were followed for an average of 14 months, with 22%, 25%, and 19% showing fixed, reversible, or combined thallium defects, respectively. Normal thallium scans were found in 34% of patients. The presence of jeopardized viable myocardium detected by dipyridamole-thallium imaging was predictive of future cardiac events (Figure 1). Patients with normal thallium images had very benign outcomes with no significant cardiac events. Patients with only fixed defects also had very benign outcomes, much like those patients with normal thallium studies. In contrast, patients with transient defects or combined transient and fixed defects showed a greater incidence of cardiac death or myocardial infarc-

A larger study by Hendel and colleagues 18 found that an abnormal dipyridamole-201Tl study was an independent predictor of death or infarction and that ²⁰¹Tl redistribution significantly increased the risk of a cardiac event.

Postmyocardial infarction risk stratification:

Following myocardial infarction, patients may appear clinically stable despite the presence of severe coronary disease. Management decisions are based on identifying patients with significant residual jeopardized myocardium, because these patients

TABLE I Prognostic Value of Thallium-201 Imaging in Patients with Known or Suspected Coronary Artery Disease

		Patients (n)	Mean Follow-up (mo)	Data Available					Significant Multivariate Predictors of Cardiac Events*	
	Type of Stress			Clinical	Stress ECG	Catheterization	201 T	Cardiac Events	201 T I	Other
Brown et al ⁷	Ex	100	46	+	+	+	+	CD, MI	Number of TD	None
Ladenheim et al ⁸	Ex	1689	12	+	+	0	+	CD, MI, CABG	Number of TD [1] Severity of PD [2]	%MPHR [3]
Staniloff et al ⁹	EX	819	12	+	+	0	+	CD, MI, CABG	Severity of PD [1] Presence of TD [2] Number of PD [3] Number of TD [4]	ST ↓ [6] Ex duration [5]
Iskandrian et al ¹⁰	Ex	743	13	+	+	0	+	CD, MI	Number of PD	None
Iskandrian et al ¹¹	Ex	196	15	+	+	0	+	CD, MI	Number of PD	None
Felsher et al ¹²	Ex	123	21	+	+	0	+	CD, MI	Abnormal scan	None
Iskandrian et al ¹³	Ex	449	25	+	+	0	+	CD, MI	PD [1] MTD [2]	None
Gill et al ¹⁴	Ex	467	91	+	+	0	+	CD, MI, CABG	↑ Lung uptake [1]	Typical AP [2] Prior MI [3] ST ↓ [4]
Kaul et al ¹⁵	Ex	293	64	+	+	+	+	CD, MI, CABG	Lung: heart ratio [1]	Diseased vessels [2 Gender [3] ΔHR [4]
Kaul et al ¹⁶	Ex	383	55	+	+	+	+	CD, MI, CABG	Number of TD [4]	Diseased vessels [1 ΔHR [2] VEA w/ex [3] β Blocker use [5]
Younis et al ¹⁷	DP	107	14	+	+	+	+	CD, MI CD, MI, UA, CABG	Combined TD + FD TD	None None
Hendel et al ¹⁸	DP	516	21	+	+	0	+	CD, MI	PD TD > 1 segment with TD Combined TD + FD	CHF DM
Stratmann et al ²	AtP	195	19	+	+	0	+	CD, MI	TD† Abnormal scan	CHF†

*Numbers in brackets indicate rank order of significant multivariate predictors when more than 1. One study did not rank all significant multivariate variables.

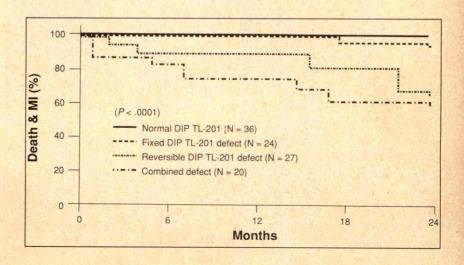
*This study did not perform multivariate analysis²; variables listed are significant univariate predictors.

AP = angina pectoris; AtP = atrial pacing; CABG = coronary artery bypass graft surgery; CD = cardiac death; CHF = congestive heart failure; Δ HR = change in heart rate during exercise; DM = diabetes mellitus; DP = dipyridamole-induced coronary vasodilation; ECG = electrocardiogram; Ex = exercise; FD = fixed defect; MI = myocardial infarction; MPHR = maximal predicted heart rate; MTD = multiple coronary vascular territory defects; PD = perfusion defect; ST \(\preceq = ST \) segment depression; TD = transient defects; \(^{20} \) TI = thallium 201; Data from Brown.

Data from Brown.

Data from Brown.

FIGURE 1. Incidence of death or myocardial infarction (MI) in 107 asymptomatic patients with coronary artery disease stratified by intravenous dipyridamole (DIP)stress thallium (TL) scintigraphy results. A reversible or combined thallium defect significantly increased the risk of this end point (p < 0.0001). (Reprinted with permission from J Am Coll Cardiol. 17)



may benefit from invasive treatment or aggressive medical therapy. The challenge is to identify those patients who are likely to experience future cardiac events, so that appropriate evaluation and treatment can be performed as soon as possible.20 The degree of postmyocardial risk is related to a number of predictors, including residual left ventricular function and the degree of jeopardized myocardium. Both the extent and the severity of exerciseinduced myocardial hypoperfusion have been shown to relate independently to the risk of cardiac events.21 Assessment of these parameters, which reflect the overall magnitude of myocardium at risk, facilitates stratification of patients into highand low-risk cohorts for subsequent cardiac events.8 Identifying high-risk patients is important for appropriate selection of therapeutic options designed to improve prognosis. Identifying low-risk patients may reduce the number of unnecessary procedures and decrease hospital costs.

Risk stratification prior to discharge has become standard practice, in part because the greatest risk of death after acute myocardial infarction occurs early. Gimple et al²⁰ demonstrated that in 36 patients discharged from the hospital after acute myocardial infarctions, 6 of the 8 cardiac events occurred within the first 6 weeks and were predicted by predischarge testing. If all tests had been performed after the initial 6 weeks, 75% of the events would have been missed. The value of predischarge testing has been demonstrated in several studies. 19,22-25 Submaximal exercise and dipyridamole-thallium testing offer particular clinical advantages in the postmyocardial setting.

SUBMAXIMAL EXERCISE TESTING: Several studies have shown that predischarge submaximal exercise testing can identify high- and low-risk cohorts in patients after myocardial infarction. 22-24,26 In addition, postinfarction exercise 201Tl imaging offers several clinical advantages compared with predischarge exercise electrocardiography: (1) increased sensitivity for detecting multivessel coronary disease; (2) the ability to localize ischemia to individual coronary territories; (3) the ability to distinguish infarct from noninfarct zone myocardium; and (4) the ability to identify exercise-induced left ventricular dysfunction, manifested by increased lung uptake.1

Gibson and colleagues²⁶ evaluated the prognostic value of predischarge submaximal exercise 201Tl imaging in patients with an acute myocardial infarction. High-risk 201Tl indices, including 201Tl redistribution, defects involving multiple vascular territories, and increased lung uptake, had the best

predictive value for cardiac events compared with stress electrocardiographic and cardiac catheterization data.

DIPYRIDAMOLE-THALLIUM-201 FOR EARLY POST-MYOCARDIAL INFARCTION RISK STRATIFICATION: Although exercise ²⁰¹Tl imaging seems to have a relatively high sensitivity for the detection of underlying coronary artery disease and future cardiac events, dipyridamole-thallium imaging may have a particular advantage in early risk stratification after myocardial infarction. Young et al27 demonstrated that 201Tl imaging during coronary hyperemia induced by dipyridamole has improved sensitivity for coronary disease compared with submaximal exercise ²⁰¹Tl imaging.

Leppo et al²⁸ evaluated the prognostic value of predischarge dipyridamole-thallium imaging in 51 patients 7–10 days following infarction. They compared thallium predictors to a number of other clinical variables, including location of infarction and left ventricular ejection fraction. The presence of thallium redistribution as a marker of jeopardized viable myocardium was the only significant predictor of cardiac events, with endpoints of death or reinfarction. Importantly, Leppo et al28 also found that the sensitivity for detecting cardiac events was greater than standard submaximal exercise testing. Of the 26 patients who underwent both dipyridamole-thallium and submaximal exercise, 13 had cardiac events. Of that subgroup, only 46% had positive stress electrocardiogram tests, whereas 12 of the 13 showed evidence of thallium redistribution.

Moreover, dipyridamole has several advantageous properties that allow dipyridamole-thallium imaging to play an important role in early inhospital management of acute myocardial infarction. Unlike exercise, dipyridamole-201Tl studies produce only modest changes in heart rate and blood pressure²⁹⁻³¹ but provide superior images compared with resting studies, with a sensitivity for coronary disease equal to that of maximal exercise ²⁰¹Tl imaging. ^{29,30,32–34} In addition, the hemodynamic effects of dipyridamole are short lived when used intravenously, and dipyridamole-induced ischemia is rapidly reversed with theophylline.

Thus, dipyridamole-201Tl imaging may be particularly well suited for risk stratification of patients within the first few days after acute myocardial infarction, and the clinical impact is clear: the earlier such risk stratification can be applied, the earlier management decisions can be made. This not only reduces hospital costs, but may prevent in-hospital cardiac events.

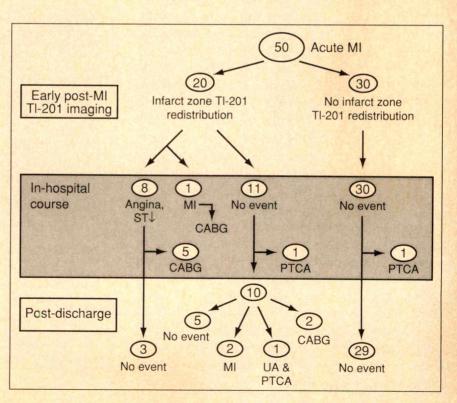
Brown and colleagues²⁵ recently reported a series of 50 patients who underwent dipyridamole-²⁰¹Tl imaging 1–4 days (mean 2.6) postinfarction. Half of the patients had received thrombolysis treatment. No patient had a serious adverse effect from the protocol. The prognostic value of ²⁰¹Tl, electrocardiographic, clinical, and cardiac catheterization data was compared using multivariate analysis. Infarct zone ²⁰¹Tl redistribution was the only significant predictor of in-hospital cardiac events: 9 of 20 patients with infarct-zone ²⁰¹Tl redistribution had in-hospital cardiac events, compared with 0 of 30 patients without infarct-zone redistribution (Figure 2). During a 12-month mean follow-up, 3 more patients with infarct-zone redistribution had cardiac events compared with none without redistribution (Figure 2). Thus, dipyridamole-201Tl imaging can identify a group of patients at high risk for early and late cardiac events who are most likely to benefit from revascularization. Similarly, patients at low risk who may be candidates for early discharge can be identified.

LATE POSTMYOCARDIAL INFARCTION: Exercise ²⁰¹Tl scintigraphy is also useful in predicting future cardiac events in patients who present with recurrent angina late (postdischarge) after prior myocardial infarction.³⁵ The presence of infarct-zone ²⁰¹Tl redistribution was found to have superior prognostic value compared with other patient variables, including clinical, electrocardiographic, and catheterization data.35

Preoperative risk stratification for peripheral procedures: Patients undergoing peripheral vascular surgery are logical candidates for ²⁰¹Tl imaging because they have a high prevalence of underlying, often asymptomatic coronary artery disease.36-38 Dipyridamole-201Tl imaging allows application of the imaging technique to this group of patients, who often have very limited exercise capacity due to claudication. Boucher and colleagues³⁹ screened a series of stable patients with clinical or electrocardiographic evidence of coronary artery disease (e.g., history of myocardial infarction, chest pain, or abnormal electrocardiogram) with dipyridamole-201Tl imaging before nonemergency peripheral vascular surgery. Of 16 patients with 201Tl perfusion defects that showed redistribution, 8 (50%) had perioperative ischemic cardiac events, compared with none of 32 patients with normal studies or with fixed defects only. Thus, consistent with prior studies involving other patient groups, the presence of jeopardized viable myocardium had important prognostic value.

In a subsequent study, Leppo et al⁴⁰ evaluated a series of 89 patients undergoing peripheral vascular surgery. They compared the predictive value of thallium imaging to a number of other clinical variables, including age, gender, prior infarction, angina, and diabetes. Using multivariate logistic regression, they found that the presence of thallium redistribution was the only significant predictor of infarction or death. This was true for both

FIGURE 2. Outcome in-hospital and after discharge of patients based on the presence or absence of infarct zone thallium-201 redistribution seen on early postmyocardial infarction imaging. CABG = coronary artery bypass graft surgery MI = myocardial infarction: PTCA = percutaneous transluminal coronary angioplasty; ST ↓ = ST-segment depression: TI = thallium; UA = unstable angina. (Reprinted with permission from Am J Cardiol.25)



dipyridamole—²⁰¹Tl and exercise studies. When thallium redistribution was present, 33% of the patients developed perioperative myocardial infarction or died. In contrast, when thallium redistribution was absent, only 2% experienced infarction or death.

Eagle et al41 conducted a follow-up study of 200 consecutive patients who underwent dipyridamole-²⁰¹Tl imaging before peripheral vascular disease surgery, and they identified 5 clinical risk factors including diabetes mellitus, Q waves on electrocardiography, a history of ventricular arrhythmias, a history of angina, and advanced age-that were univariate correlates of postoperative cardiac events. Dipyridamole-201Tl imaging was most helpful for risk stratification among patients with 1 or 2 clinical risk factors: 16 of 54 (30%) patients with ²⁰¹Tl redistribution had a perioperative cardiac event compared with only 2 of 62 (3%) patients without redistribution. Among other patient subgroups, 201Tl imaging was less helpful, since only 3% of patients with none of the clinical indicators had ischemic events (with no cardiac deaths), and 10 of 20 (50%) patients with 3 or more clinical markers had events. Thus, preoperative dipyridamole-thallium imaging appeared to be most useful in stratifying vascular patients determined to be at intermediate risk by clinical evaluation.

A number of studies have demonstrated that the risk of perioperative cardiac events is related not only to the presence of jeopardized myocardium, but also to its extent. Recent data from Brown and Rowen⁴² suggest that this principle extends to preoperative risk stratification as well. Among 231 patients undergoing noncardiac surgery who had preoperative thallium studies, multivariate logistic regression analysis found that the only 2 significant predictors of perioperative cardiac death or myocardial infarction were the number of segments with transient defects (an index of the extent of myocardium at risk) and a history of diabetes mellitus. Patients with no transient defects had a very low risk of perioperative infarction or death. As the number of segments with transient defects increased, the probability of developing a cardiac event increased substantially. In addition, for a given number of segments, the presence of diabetes mellitus substantially increased the risk of a cardiac event. Thus, perioperative risk is related to the presence of myocardium at risk and the perioperative risk increases as a function of the extent of jeopardized, viable myocardium.

CONCLUSION

Thallium-201 myocardial perfusion imaging has an important prognostic value in a wide spectrum of patients with coronary heart disease. Identification of the presence and extent of jeopardized viable myocardium is an important factor, independent of coronary anatomy, for formulating management decisions.

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Comparison of Thallium-201 and Technetium-99m Methoxyisobutyl Isonitrile

Frans J. Th. Wackers, MD

Thallium-201 (201TI) is a well-established radionuclide used in myocardial perfusion imaging for assessing the presence and prognostic significance of coronary artery disease. Recently, technetium-99m hexakis-2-methoxyisobutyl isonitrile (99mTc-sestamibi) has become available for the same diagnostic and prognostic procedures. This discussion compares the imaging characteristics and clinical applications of 201TI with those of 99mTc-sestamibi. There is a strong diagnostic concordance between the 2 agents in symptomatic patients. Various comparative clinical trials have shown in numerous patients that both agents have a similar diagnostic yield in both planar and single-photon emission computed tomography (SPECT) imaging. Because of better image quality of the 99mTc agent, there is a trend toward better specificity and normalcy rate, in comparison to ²⁰¹TI. However, when using reinjection imaging protocols, 201 Tretains a unique place as an imaging agent to identify viable myocardium.

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or years, investigators have searched for ways to label myocardial perfusion agents with technetium-99m (99mTc) in order to overcome some of the limitations of thallium-201 (201Tl). In particular, the low-energy photons (68–80 keV) of ²⁰¹Tl are suboptimal for standard gamma cameras, which perform best at the 140 keV photopeak of 99mTc. In addition, the long radioactive half-life (73 hours) of ²⁰¹Tl requires limited doses of 2-3.5 mCi, which results in relatively low count density and somewhat granular images.1

Despite the clinical availability of 99mTc-labeled imaging agents, however, ²⁰¹Tl remains, as it has for over a decade, the most widely used myocardial perfusion imaging agent for the diagnosis and prognosis of coronary artery disease (CAD).1,2 In particular, the clinical benefits of 201Tl and the emergence of new imaging techniques (including reinjection and pharmacologic stress imaging) have reinforced its widespread acceptance in nuclear cardiology.3-6 Moreover, 201Tl continues to enjoy a significant role as the "gold standard" to which all new perfusion agents are compared. 1,2,6

The 99mTc compound hexakis-2-methoxyisobutyl isonitrile (99mTc-sestamibi) is a relatively new radiopharmaceutical agent that has been favorably compared to 201Tl for the detection of ischemic myocardium.

Unlike ²⁰¹Tl, ^{99m}Tc-sestamibi does not redistribute significantly in myocardium after a stress injection.7 However, although it has a somewhat lower overall myocardial extraction fraction, like 201Tl, 99mTc-sestamibi distribution in the myocardium is proportional to blood flow. Uptake is linear at ranges of coronary blood flow that are 2-3 times greater than resting level, and a plateau effect is seen at higher flow rates.8

This review discusses findings of several studies comparing 201Tl with 99mTc-sestamibi and describes several recent developments that have effectively enhanced the diagnostic capability of 201Tl imaging. In particular, the 2 agents are compared in terms of image quality and diagnostic value, as well as practical clinical usage.

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TABLE 1 99mTc-Sestamibi: Diagnosis of Coronary Artery Disease and Comparison with Coronary Angiography

			Sensitiv	vity	Specificity		
Reference	Imaging*	No.	Sestamibi (%)	²⁰¹ Tl (%)	Sestamibi (%)	²⁰¹ TI (%)	
Kiat ¹	Р	19	73	73	†	t	
Taillefer ⁹	P	65	70	74	†	†	
Wackers ²	P	36	89	97	†	†	
Multicenter USA§	Р	195	86	88	89‡	53‡	
Multicenter Int. A§	P	80	89	91	†	†	
Multicenter Int. B§	Р	162	95		78		
Kiat ¹	S	19	93	80	†	†	
Iskandrian ¹⁰	S	39	82	82	100	82	
Kahn ¹¹	S	38	95‡	84‡	†	†	
Multicenter USA§	S	192	89	90	49	41	
Multicenter Int. A§	S	81	93	99	†	t	
Multicenter Int. B§	S	85	87	-	1	- T	

*Planar (P) or single-photon emission computed tomography (S) \dagger = Not meaningful. \dagger p < 0.05. \dagger planar dished observations.

SENSITIVITY AND SPECIFICITY COMPARISONS

In a multicenter trial of 33 patients referred for evaluation of chest pain, Taillefer et al⁷ found a strong agreement between 201Tl and 99mTc-sestamibi, both on a segment-by-segment and on a patientby-patient basis.

Qualitative assessment of 201Tl and 99mTcsestamibi distribution was performed in 297 left ventricular segments. There was good correlation between the 2 radiopharmaceuticals for the presence of normal, scarred, or ischemic tissue. On a segment-by-segment basis (3 segments on each of 3 views), the agreement was 87.2% (259 of 297); on a patient-by-patient basis, it was 87.9% (29 of 33). The number of segments found ischemic with the 2 compounds were nearly equal, as were the number that were normal with one and ischemic with the other. This study indicates that 201Tl and 99mTcsestamibi are equally accurate in the detection of stress-induced myocardial perfusion defects.

Wackers et al² evaluated the biodistribution, dosimetry, and safety of 99mTc-sestamibi in 17 normal volunteers at rest and exercise in Phase I of a multicenter study. The study established that 99mTc-sestamibi exhibits rapid blood clearance, good myocardial uptake, and favorable target-tobackground ratios for myocardial perfusion imaging. Dosimetry allows for administration of up to 30 mCi of the radionuclide.

Phase II of this study compared detection rates of significant CAD by 201Tl and 99mTc-sestamibi stress or rest imaging. Of 36 patients with significant CAD, 35 (97%) had abnormal ²⁰¹Tl stress images and 32 (89%) had abnormal ^{99m}Tc-sestamibi stress images (p = not significant). 99mTcsestamibi images correlated in 31 of 35 patients (86%) who had either scar or ischemia on ²⁰¹Tl images. On a segment-to-segment basis, exact concordance was obtained in 463 of 570 myocardial segments (81%). Thus, the detection rates for significant coronary artery disease were similar with the 2 radionuclides, and no significant differences were observed for either the overall detection of disease or the detection of disease in specific vascular territories.²

Subsequently, numerous studies have demonstrated that there is no significant difference between the two imaging agents in terms of sensitivity and normalcy rates for single photon emission computed tomography (SPECT) and planar imaging (Table I). 1,2,9-11

In a multicenter trial of approximately 200 patients, the sensitivities of planar and SPECT imaging were similar with both 201Tl and 99mTcsestamibi (unpublished observations).

IMAGE CHARACTERISTICS

Wackers et al² also concluded that the quality of the images obtained by both 201Tl and 99mTcsestamibi was good in all normal subjects. Myocardial visualization on stress or redistribution ²⁰¹Tl images and on stress or rest 99mTc-sestamibi images was comparable. The 99mTc-sestamibi images, however, were somewhat more "crisp" and less granular; this is probably due to the fact that the 99mTc-sestamibi images have less low-energy scatter than those obtained with ²⁰¹Tl. During the first 60 minutes after a resting injection of 99mTc-

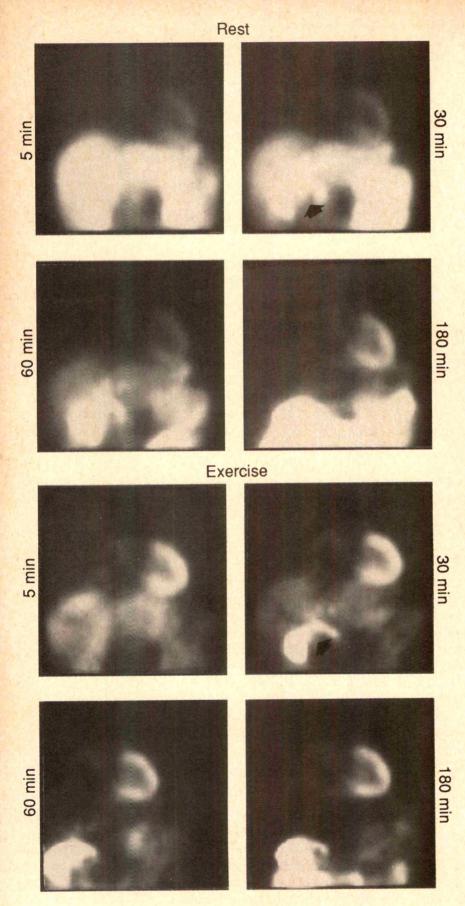
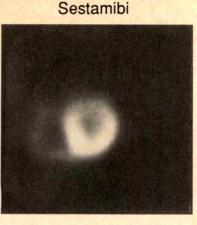
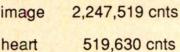


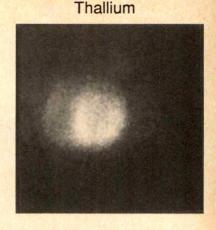
FIGURE 1 Rest: Large field-ofview anterior projections at 5, 25, 30, and 180 minutes after injection of technetium-99m [99mTc]-sestamibi at rest in a normal volunteer. The left ventricle is well visualized. However, the heart-toliver ratio improves over time by clearance of the radiotracer from the liver into the biliary system (arrow). Exercise: Large field-ofview anterior projection after injection of 99mTc-sestamibi at peak exercise in a normal volunteer. The left ventricle is well visualized at all times. Compared with the injection at rest, substantially less liver uptake of radiotracer is present. (Reprinted with permission from J Nucl Med.2)

FIGURE 2. Left anterior oblique planar images from the same patient with technetium-99m sestamibi and thallium. The sestamibi image was acquired in 5 min and the ²⁰¹TI image in 10 min. Note the difference in image quality and

count density. cnts = counts.







501,834 cnts 105,409 cnts

sestamibi (Figure 1A), the heart was well visualized despite a marked accumulation in the liver and spleen. After an exercise injection (Figure 1B), there was excellent visualization of the heart with substantially less uptake in the liver and spleen.

Figure 2 shows a comparison of left anterior oblique planar images from the same patient with ^{99m}Tc-sestamibi and thallium. The thallium image was acquired with a dose of 2.5 mCi for 10 minutes; for ^{99m}Tc-sestamibi 20 mCi was injected and the image was acquired for 5 minutes. Both images were of good quality for each agent. Myocardial visualization on the ^{99m}Tc-sestamibi image was similar to that on the ²⁰¹Tl image. The count density in the heart on the ^{99m}Tc-sestamibi image is higher than on the ²⁰¹Tl image.⁷ The ^{99m}Tc-sestamibi image was less granular and had sharper edges, however, resulting in better myocardial wall definition.

99mTc-sestamibi has demonstrated adequate myocardial extraction and a greater myocardial retention than thallium, resulting in higher count density and superior image quality. However, the significant subdiaphragmatic activity with 99mTcsestamibi occasionally has been shown to interfere with analysis of inferior myocardial wall uptake, especially in images obtained within 1 hour after injection of 99mTc-sestamibi.2 Although it was suggested that images may be improved by having the patient drink milk or eat during the hour after injection, this was not confirmed in a recent systematic analysis. 12 Although images obtained with 99mTc-sestamibi were aesthetically more pleasing than those obtained with ²⁰¹Tl, there is no evidence that 99mTc-sestamibi images provide clinically superior diagnostic information compared with images obtained with thallium.

CLINICAL IMPLICATIONS

The prognostic value of redistribution imaging has been investigated in several studies. ^{13–15} These studies have shown that transient ²⁰¹Tl defects (i.e., defects that show redistribution) predict future cardiac events because they reflect the presence of jeopardized or hypoperfused viable myocardium. Since the ^{99m}Tc isonitriles do not redistribute in the myocardium and require 2 separate injections at rest and exercise, ⁷ they cannot provide comparable insight into regional myocardial blood flow and viability after a single injection. Prognostic data on ^{99m}Tc-sestamibi imaging are not yet available.

A recent study by Cuocolo et al¹⁶ compared ²⁰¹Tl stress, redistribution, and reinjection imaging with ^{99m}Tc-sestamibi imaging during stress and rest. This study indicated that ^{99m}Tc-sestamibi images consistently underestimated viable myocardium in comparison to the ²⁰¹Tl reinjection protocol.

The unique diagnostic information derived from the kinetics of ²⁰¹Tl can be illustrated in, for example, a patient with a known prior myocardial infarction, severe left ventricular dysfunction, and anginal chest pain. A resting injection with ^{99m}Tc-sestamibi will show a defect. However, how much is infarction and how much is ischemic but viable? A resting injection with ²⁰¹Tl will also show an initial defect. However, over time the defect may become smaller as ²⁰¹Tl is accumulated in ischemic but viable myocardium by redistribution. Thus, infarcted myocardium can be differentiated from hibernating myocardium.

CONCLUSION

The implication of the data discussed herein is that 99mTc-sestamibi and 201Tl provide similar diagnostic information on the presence or absence of coronary artery disease. At this time, the available information in the literature supports the preferential use of 201Tl for assessing viability. Little information exists on the role of 99mTcsestamibi in studying myocardial viability, although at the cellular level accumulation of sestamibi is at least partly dependent on viability. 17,18 The unique kinetics of 201Tl provide clinicians with important pathophysiologic information and allow assessment of blood flow and viability. Initial imaging immediately after thallium injection indicates myocardial blood flow, and redistribution imaging indicates myocardial viability.

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A Symposium: Coronary Artery Disease: Mechanisms for Myocardial Protection

GUEST EDITOR:

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The American Journal Cardiology

Introduction

Peter F. Cohn. MD

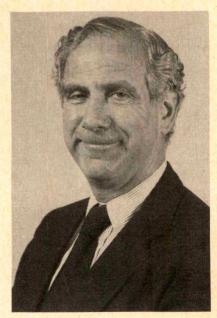
oted investigators in cardiovascular disease gathered to examine new data on ischemic heart disease and related disorders at a symposium sponsored by the Council on Myocardial Ischemia and held in December 1991 in Aventura, Florida. It was the hope of council members that the ideas generated at this conference could be translated into guidelines for practicing physicians. The information presented at that meeting is the source of this supplemental issue.

In the first article, based on his opening presentation, David Sheps reviews the relation between hypertension and diminished sensitivity to noxious stimuli. Although an association between the two has been well described in animals and tentatively demonstrated in humans, its nature remains largely unknown. Evidence from electrophysiologic, pharmacologic, and behavioral research suggests that this relation reflects an interface between the cardiovascular- and pain-regulating functions of the baroreceptor system. Sheps' study has furnished preliminary evidence that hypertensive subjects exhibit enhanced levels of circulating endorphins and diminished sensitivity to noxious thermal stimuli, which suggests that endogenous opioids may be one of many factors that contribute to the relation between blood pressure and sensitivity to

In recognition of the strong influence that calcium fluxes have on the physiologic processes and responses in the body, Arnold Schwartz discusses the molecular and cellular aspects of calcium channel antagonism. Over the past few years, L-type calcium channels and their blockade with calcium channel antagonists have become better understood. Although the application of molecular genetics to cardiovascular issues is a comparatively recent development, the area is providing insights into the molecular pharmacology of calcium antagonists.

As heart transplant recipients live longer, an accelerated and distinct form of coronary artery disease (CAD) develops and adversely affects survival. James B. Young offers his perspective on this unique form of ischemic heart disease, cardiac allograft arteriopathy. Possibly the primary factor limiting long-term survival after heart transplantation, allograft arteriopathy is quite different from the obstructive process seen in native CAD. The process may be controlled more successfully when the mechanism of cellular proliferation is better defined and the causative factors are identified.

According to Jerome Cohen, evidence from the Multiple Risk Factor Intervention Trial (MRFIT) on silent myocardial ischemia and cardiovascular risk suggests that diuretic-related hypokalemia may



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predispose patients with silent myocardial ischemia to potentially fatal arrhythmias and that use of potassium-sparing antihypertensive regimens be considered in high-risk hypertensive patients.

Through review and assessment of the results of recent studies, Prakash C. Deedwania and Enrique V. Carbajal evaluate the role of myocardial oxygen demand in the pathogenesis of silent myocardial infarction. Heart rate increases during exercise testing according to the gradual work load increments of the National Institutes of Health protocol were compared with ischemic events of daily life monitored by ambulatory electrocardiography; the two were found to be closely related. In most silent ischemic episodes recorded in these studies, heart rate and blood pressure increased significantly, indicating that increased myocardial oxygen demand is a significant pathogenic factor in silent myocardial ischemia of daily life. Review of the available data clearly demonstrates that as in anginal episodes, most silent ischemic episodes are preceded by significant increases in heart rate and/or systolic blood pressure.

The role of intracoronary ultrasonography in assessing pharmacotherapy for myocardial ischemia is discussed by Morton J. Kern. This technique can provide morphologic and physiologic information on coronary vasomotor responses to pharmacotherapy. Furthermore, preliminary studies indicate a high correlation between dimensions determined by two-dimensional echocardiography, angiography, and pathology. Similarly, the emerging data on intracoronary Doppler flow velocity responses beyond atherosclerotic obstructions before, during, and after coronary balloon occlusion will provide further insights into myocardial oxygen supply and its responses to pharmacotherapy during controlled myocardial ischemia.

The prevalence and prognostic significance of transient myocardial ischemia after coronary artery bypass grafting (CABG) are evaluated by Donald A. Weiner. Results from earlier studies have shown that exercise testing often produces inaccurate indications of the effectiveness of CABG revascularization. More recent studies demonstrate that ischemia—usually silent—occurs frequently after CABG. Although the mechanisms underlying the occurrence of silent myocardial ischemia after CABG are unknown, they may have a neurogenic basis or result from a reduction in the amount of jeopardized myocardium after successful revascularization. Conflicting results have been produced in studies analyzing the prognostic significance of postoperative ischemia. Many treatment approaches, including the use of antianginal medications, coronary artery angioplasty and a second CABG, can successfully lessen or eliminate ischemia. The best strategy for lowering the risk of adverse cardiac events among patients with postoperative ischemia remains uncertain at present.

In their annual reports, the council's advisory groups review ongoing research in silent ischemia, acute intervention, and postinfarction management. Research continues to be directed toward whether or not treatment can affect the negative prognosis associated with silent myocardial ischemia. In addition, the traditional role of digoxin in treatment of atrial fibrillation has been reexamined because of the increased number of pharmacologic options available for heart rate control.

Finally, two case studies on myocardial ischemia are discussed under the leadership of William W. Parmley and Jay M. Sullivan. The diagnostic and therapeutic highlights of these peer-group discussions constitute the concluding segment of this special issue of The American Journal of Cardiology.

Relation Between Systemic Hypertension and Pain Perception

David S. Sheps, MD, MSPH, Edith E. Bragdon, MA, T. Flint Gray III, MD, Martha Ballenger, James E. Usedom, MD, and William Maixner, DDS, PhD

To test the hypothesis that hypertension diminishes pain perception, a study was made that evaluated the relation between arterial blood pressure and thermal pain perception in human subjects. The average mean arterial pressure in all 20 men studied (10 hypertensive, 10 normotensive) proved to be significantly related to both thermal pain threshold (p = 0.05) and tolerance (p = 0.003). The difference between normotensive and hypertensive groups in baseline and posttest plasma levels of β endorphin was also significant (p = 0.02) and indicated an interaction between endogenous opioids and blood pressure. Other recent studies of hypertension in relation to hypalgesia were also reviewed. An increased pain threshold was found in hypertensive versus normotensive rats. In cats, electrical stimulation of vagal afferent nerves (cardiopulmonary baroreceptors) suppresses nociceptive responses, and both pharmacologic elevation of blood pressure and vascular volume expansion produce antinociperception. Together with preliminary findings in human studies, these results indicate an interaction between pain-controlling and cardiovascular regulatory functions that is probably mediated by the baroreceptor system. (Am J Cardiol 1992;70:3F-5F)

number of experimental findings in animals demonstrate an association between hypertension and diminished sensitivity to noxious stimuli. Several investigators have reported an increased thermal pain threshold in hypertensive versus normotensive rats, as measured by the hot plate technique. 1-3 Interestingly, this hypalgesia is reversed by the opioid antagonist naloxone, 2,3 which implies that the relation between blood pressure and pain perception is at least partly modulated by endogenous opioids. Elevated mechanical pain thresholds have also been seen in spontaneously hypertensive rats.4

Studies in humans, although less extensive than in animals, also appear to link hypalgesia and elevated blood pressure. For example, Zamir and Shuber⁵ and Ghione et al⁶ demonstrated higher pain thresholds in hypertensive subjects than in normotensive controls in response to electrical stimulation of tooth pulp.

METHODS

Although the assessment of pain perception with electrical and mechanical stimuli has provided useful information, it has not been clarified whether hypertension diminishes pain perception evoked by procedures that selectively stimulate nociceptive afferents.

An alternative approach is to apply noxious thermal stimuli that selectively activate peripheral nociceptors. Sensitivity to thermal pain can be measured with a computer-controlled, hand-held thermal probe that a technician places on the volar forearm of a research subject. In our laboratory, investigators have delivered thermal stimuli ranging from 43° to 50°C in 0.5°C steps of 5 seconds each. Subjects were instructed to report when they first perceived the stimulus as painful (threshold) and again when they perceived the stimulus as intolerable (tolerance); at the latter point, the device was removed. Three ascending series of thermal stimuli were delivered to 3 separate loci on the volar forearm, and the average temperature

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TABLE I	Properties of Mechanoreceptors Associated with	
Cardiova	scular Regulation	

Location	Afferent Nerve	Stimulus	Response
Carotid sinus	IX	↑ Arterial pressure	↓ Sympathetic tone ↑ Parasympathetic tone Δ EEG synchronization ↓ "Sham rage" behavior
			↓ Somatomotor reflexes (? analgesia)
Aortic arch	X	↑ Arterial pressure	↓ Sympathetic tone↑ Parasympathetic tone
Cardiopul- monary region	X	↑ Vascular volume ↑ Central venous pressure	↓ Sympathetic tone ↑ Parasympathetic tone Δ EEG synchronization ↓ Somatomotor reflexes
		Opiates Nicotine	(? analgesia)
		Veratrum alkaloids Serotonin	
		Capsaicin	

values associated with threshold and tolerance were determined.

We used this technique to test thermal pain perception in 20 nonmedicated men (mean age 34 ± 13 years) of whom 10 were hypertensive (blood pressure $\geq 140/90$) and 10 normotensive. Blood pressure was continuously monitored by an automated cuff during testing. Blood samples were drawn at baseline after a rest period and immediately after testing, and were assayed by a highly

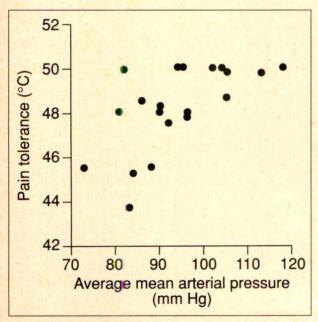


FIGURE 1. Relation between average mean arterial pressure (mm Hg) during thermal pain perception testing and tolerance to thermal pain ($^{\circ}$ C) in 20 nonmedicated men (r = 0.635; p = 0.003).

sensitive and specific immunoreactive technique for β endorphin concentrations.

RESULTS

In all subjects, the average mean arterial pressure during testing was significantly related (by regression analysis) to both the thermal pain threshold (r = 0.44; p = 0.05) and tolerance (r = 0.635; p = 0.003) (Figure 1). The baseline and posttest plasma levels of β endorphin in the normotensive group were significantly different from those of the hypertensive group (p = 0.02). However, a direct relation between pain perception and circulating endorphin levels was not observed, possibly because of the small size of our sample.

DISCUSSION

These findings not only provide further evidence of a relation between hypertension and diminished pain perception, but also support the existence of a specific interaction between the endogenous opioid system and pain-blood pressure regulatory systems. The nature of this interaction has not been well explored, but it may be mediated by the baroreceptor system of cardiovascular regulation. ^{1–3,8}

The baroreceptor reflex arcs are activated by stimulation of mechanoreceptors (Table I): pressure receptors, located in the carotid sinus and aortic arch, whose afferents travel via cranial nerves IX and X; and volume receptors, located in the cardiopulmonary region, whose afferents travel via cranial nerve X (the vagus). The pressure receptors are sensitive to increased arterial pressure, whereas the volume receptors are sensitive to increases in vascular volume. The baroreceptors respond to these stimuli by decreasing sympathetic tone. Also, the activation of these visceral afferents alters central nervous system excitability, promoting electroencephalographic synchronization, sleeplike behavior, a suppression of "sham rage," and behavioral responses consistent with analgesia.8-11

Electric stimulation of vagal afferent nerves in cats has been shown to suppress nociceptive reflexes—for instance, inhibiting the normal response of dorsal horn neurons to painful stimuli in their receptive fields. ^{9,12} Similarly, pharmacologic elevation of blood pressure ^{8,11} (for example, by phenylephrine) and cardiovascular volume expansion ¹³ induce attenuation of the tail-flick reflex (an index of algesia) in animals.

The enhanced cardiopulmonary baroreceptor activity associated with hypertension may mediate

the hypalgesia found in hypertensive subjects. 14,15 In support of this hypothesis, the hypalgesia found in hypertensive rats can be attenuated by interruption of the right cervical vagus nerve and, conversely, is enhanced by increasing vascular volume and central venous pressure. 13

Although the role of endogenous opioids in the integration of the pain and cardiovascular regulatory systems is not yet clear, their participation is suggested by a number of facts. First, various sites within the central nervous system that are involved in arterial blood pressure regulation also contain opioid receptors and are known to mediate analgesia, which in some instances is reversible by naloxone. Next, injection of B endorphin into the nucleus tractus solitarii, which receives afferent fibers from the vagus, decreases arterial blood pressure and heart rate in rats, an effect that can be blocked by prior administration of naloxone.16 Further, recent evidence suggests that endogenous opioids may act peripherally as well as in the central nervous system to blunt the activation of pain reflexes in animals, in part by stimulating cardiopulmonary vagal afferents. 17,18

The antinociceptive effects that accompany blood pressure elevation may eventually contribute to the development of essential hypertension.^{3,8} The consequent relief from aversive sensations that are evoked by environmental stressors may invoke conditioning mechanisms that gradually modify the short-term coping pattern of acute blood pressure reactivity into chronic disease. Such mechanisms may utilize endogenous opioids as part of a reward system.

CONCLUSION

An association between hypertension and hypalgesia has been well described in animals and tentatively demonstrated in human subjects, although its nature remains largely unknown. Evidence from electrophysiologic, pharmacologic, and behavioral research suggests that this relation reflects an interface between cardiovascular and pain-regulating functions of the baroreceptor system. Endogenous opioids influence baroreflex ac-

tivity, and a number of measures of pain perception fluctuate in response to opioid production. Further, the results of our study furnish preliminary evidence that hypertensive subjects exhibit enhanced levels of circulating endorphins and diminished sensitivity to noxious thermal stimuli. Hence, endogenous opioids may be one of many factors that contribute to the relation between blood pressure and sensitivity to pain.

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Molecular and Cellular Aspects of Calcium Channel Antagonism

Arnold Schwartz, PhD, DSc (Hon)

Calcium fluxes play a key role in controlling many physiologic processes and responses in the body. The past few years have witnessed major advances in understanding of L-type calcium channels and their blockade with calcium channel antagonists. The L-type calcium channels comprise 5 subunits termed α_1 , α_2 , β , γ , and δ . Elucidation of the mechanisms of action of the calcium channel antagonists has been advanced by cloning and genetic manipulation of these subunits. The α_1 subunit appears to be responsible for channel opening and voltage dependency, and it contains receptors for calcium channel antagonists; these geographically distinct receptors correspond to each of the 3 different chemical classes of antagonists, exemplified by diltiazem, nifedipine, and verapamil. Diltiazem appears to have an inhibitory effect on mitochondrial sodium-calcium exchange that is unique among calcium channel antagonists. Preliminary data suggest that a diltiazem-specific receptor also exists in the endothelium. It appears, therefore, that despite advances in the understanding of L-type calcium channels, much remains to be learned about other possible receptors for the calcium channel antagonists.

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ost calcium channel antagonists currently approved by the U.S. Federal Drug Administration belong to 3 distinct chemical classes: the phenylalkylamines (e.g., verapamil), the dihydropyridines (e.g., nifedipine), and the benzothiazepines (e.g., diltiazem). Receptors specific for each of these 3 major classes have been identified in the L-type (long-lasting, large capacitance) voltage-dependent calcium channels. Since the maintenance of intracellular and extracellular concentrations of calcium is crucial for the proper function of tissues and organ systems, calcium antagonists have been used selectively to manage a variety of cardiovascular and cerebrovascular disorders. The primary purpose of this article is to present current knowledge of the binding of these antagonists to the calcium channel. However, data that suggest additional intracellular actions for these agents will also be reviewed.

MOLECULAR BIOLOGY OF CALCIUM CHANNELS

Calcium is the key messenger in initiating muscular contraction, and several types of calcium channels exist for transmission of the ion across the cell wall. Most studies have concentrated on the so-called L-type voltage channel, the channel that is most responsive to the calcium antagonists. L-type channels in skeletal muscle are relatively insensitive to these drugs; that is, they are pharmacologically inactive or unresponsive. The L-type channels most sensitive to calcium antagonists are located in vascular smooth muscle, the sinoatrial node, the atrioventricular node, certain specialized conducting tissues, and cardiac muscle tissue.²

The data that have accumulated thus far support the view that the L-type calcium channel consists of 5 subunits termed α_1 , α_2 , β , γ , and δ . Use of photoaffinity labels in the laboratories at the University of Cincinnati and elsewhere showed that the receptors corresponding to each of the 3 major classes of calcium channel antagonists are all located on the α_1 subunit, which is the largest calcium channel subunit.3

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Structure–function relations: A recent development is the ability to clone the genes for the L-type calcium channel subunits, an advance that prompted intensive research into structure–function relations. At the University of Cincinnati, the α_1 subunit has been cloned from several different tissues, including heart, vascular smooth muscle, and brain.⁴ This subunit is arranged in 4 repeating hydrophobic motifs, with each motif consisting of 6 segments that span the cell membrane (Figure 1).⁵

Using an α_1 subunit from cardiac muscle, Tanabe et al⁶ replaced the loop between motifs 2 and 3 with the corresponding loop from skeletal muscle. The resulting chimera exhibited excitation-contraction characteristics of skeletal muscle calcium channels (i.e., relatively fast) rather than that of cardiac muscle (i.e., relatively slow). This finding represented a major advance in our understanding, since it was the first identification of a structure-function relation in this subunit. Other properties of this subunit, such as voltage sensing, pore formation, drug binding, and metabolic regulation, may also be correlated with specific regions in the near future. For example, in each motif, one of the transmembrane segments (the fourth) is a region of charged amino acids (Figure 1). It has been hypothesized that this fourth segment forms the voltage sensor for the calcium channel and is involved in opening and closing of the channel.⁵

Subunit interactions: Using cloned subunits, researchers at the University of Cincinnati showed that the other calcium channel subunits may be important in modulating peak current and gating. Coexpression of the α_1 and α_2 subunits increased peak current amplitude above that seen in the α_1 subunit alone. Coexpression of the α_1 , β , and δ subunits, or α_1 and β subunits, produced a leftward shift in the voltage of activation. Most important, the presence of the β subunit caused the channel to assume kinetics that closely resembled native calcium channels. These data suggest that calcium

channel activity is strongly modulated by the β subunit via effects on both activation and inactivation kinetics of the channel.

From the clinical perspective, perhaps the most important issue concerns modulation of drug binding. As already mentioned, the binding sites for the 3 classes of calcium antagonists are located on the α_1 subunit. Preliminary data from our laboratory suggest that, in skeletal muscle, other subunits are also involved in drug binding, although their specific roles are still unknown.

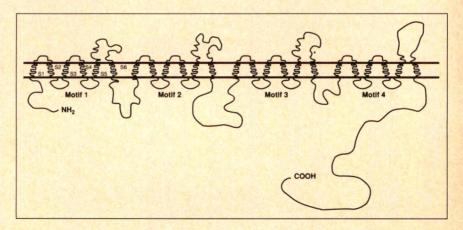
Diversity of L-type channels: It is now appreciated that there is a tremendous diversity in L-type calcium channels. While only 2 skeletal muscle isoforms have been found, the heart, aorta, lung, and brain have each been shown to contain several different isoforms. Genomic cloning has revealed that some of these isoforms are the product of different genes. For example, multiple genes have been identified for α_1 subunits. It has been proposed that the cardiac and smooth muscle subunits are encoded by the same gene, whereas the skeletal muscle isoform is encoded by another, distinct gene.

Another level of diversity appears to be provided by alternatively spliced subunit elements. In cardiac muscle and in smooth muscle, variants have been observed in the α_1 subunit, with the points of variation occurring at the termini, at motif 1, and at motif 4 (Figures 1 and 2). In the brain, alternative splicing may account for as many as 6 variant calcium channels.

PROTECTION OF ISCHEMIC CARDIAC MYOCYTES

During myocardial ischemia, calcium channels open to allow a surge of ions into the cell. Adenosine triphosphatase malfunction causes increased levels of intracellular sodium leading to sodium—calcium exchange, which further adds to the level of calcium within the cell. As ischemia progresses,

FIGURE 1. Schematic representation of the L-type calcium channel. S1 to S6 represent transmembrane segments of the protein. The S4 segment in each motif contains a region of charged amino acids that is hypothesized to be the voltage sensor of the calcium channel. (Reprinted with permission from Hypertension.⁴)



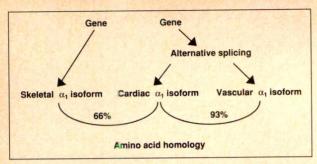


FIGURE 2. Sources of diversity for α_1 isoforms. One gene encodes the skeletal isoform, another encodes cardiac and vascular isoforms. Variants can also be produced by alternative splicing. The approximate percentage of homology in amino acid sequences between these isoforms is noted.

levels of phosphate also rise and, eventually, calcium phosphate precipitates within the mitochondria. This latter occurrence inhibits oxidative phosphorylation and leads to swelling and structural damage.

In contrast, myocardial tissue that has been pretreated with diltiazem maintains its levels of inorganic phosphate and retains virtually all of its structural integrity. ¹⁰ As a result, the cellular energy balance is also maintained.

Other calcium antagonist classes evaluated at the University of Cincinnati have not produced comparable protection. It is possible that diltiazem and other benzothiazepine-related compounds may have an additional inhibitory action on sodiumcalcium exchange in mitochondria. Such inhibition would be expected to prevent ischemia-induced conduction delay. Further, it should be pointed out that the doses of diltiazem used in these experiments corresponded to the upper end of the dosing range in humans. 10 Studies of calcium antagonists in patients with myocardial infarction have generally used drug dosages at the lower end of the range and have produced mixed results regarding the protective effects of these agents. One exception is the Diltiazem Reinfarction Study, which used comparable diltiazem dosages.11 This study concluded that diltiazem was effective in preventing early reinfarction and severe anginal symptoms.

FUTURE DIRECTIONS

Despite advances in the understanding of Ltype calcium channels, much remains to be discovered regarding other possible receptors for calcium antagonists. For example, preliminary data suggest that a diltiazem-specific receptor also exists in the endothelium.¹²

Thus, although the application of molecular genetics to cardiovascular issues is a comparatively recent development, the area is providing insights into the molecular pharmacology of calcium antagonists. Eventually, it may provide an explanation for the differential action of these agents in various tissues and the basis for designing more agents that are tissue specific.

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Cardiac Allograft Arteriopathy: An Ischemic Burden of a Different Sort

James B. Young, MD

As heart transplant recipients live longer, an accelerated and distinct form of coronary artery disease develops that adversely affects survival. Indeed, cardiac allograft arteriopathy may be detected in as many as 90% of heart transplant recipients after 5 years. The precise incidence is not easily determined because the disease can be difficult to recognize when noninvasive tests are used; even angiography has substantive limitations. The distinct characteristics of this type of coronary artery disease result in a different form of chronic ischemic syndrome. The angiographic hallmark of allograft arteriopathy is an extensive, diffuse, obliterative process that primarily involves distal, small, subendocardial arteries. Endothelial injury seems to trigger the disease process. The arteriopathy is likely immunologically mediated and promoted or exacerbated by traditional atherosclerotic disease risk factors. Viral infection may be involved as well. To gain a better understanding of allograft arteriopathy, it is worthwhile to review its incidence, pathophysiology, prognosis, prevention, and treatment.

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bliterative disease of the coronary arteries after heart transplantation is a frequently observed phenomenon that remains a vexing enigma.^{1,2} Indeed, the first long-term survivor of this operation succumbed to complications caused by coronary artery disease (CAD).3 As patients live longer after heart transplantation, the likelihood that allograft arteriopathy will cause problems increases dramatically. Although rejection and infection remain the leading causes of death in heart transplant recipients during the first postoperative year, arteriopathy may well be the most common primary cardiac cause of death during long-term follow-up.4 The obliterative process is not necessarily unique to the coronary circulation and generally is distinct from native coronary vessel arteriosclerosis. Although many terms have been suggested for this process, including chronic rejection, accelerated graft atherosclerosis, posttransplant coronary occlusive disease, and spontaneous arteriosclerosis, allograft arteriopathy seems the most appropriate description because similar posttransplantation vascular abnormalities can be seen after kidney, liver, and combined heart/lung transplantation.²

INCIDENCE AND DETECTION

In seminal work performed at Stanford University, Gao et al⁵ found that the incidence of allograft arteriopathy can be as high as 40% at 2 years after transplantation and well over 50% at 5 years. Results of this investigation suggest that the process can be detected in virtually every transplant patient who survives more than several years. When histopathologic definitions are employed, allograft arteriopathy may be a finding on autopsy as early as 1 year after heart transplantation in patients whose angiograms appear normal.⁶

The precise incidence of allograft arteriopathy is not easily determined, since it can be difficult to recognize when noninvasive tests are used. Although angiography is most often used to diagnose arteriopathy, it also has substantive limitations. At the Multi-Organ Transplant Center, noninvasive

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 TABLE I
 Clinicopathologic Characteristics of Cardiac Allograft

 Arteriopathy
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Concentric intimal proliferation
Coronary vessels diffusely involved
Subendocardial vessels affected in particular
Elastica generally intact
Calcification of lesions unusual
Focal lesions less often observed
Rapid development
Angina rare
Noninvasive diagnosis difficult
Angiographic findings problematic

tests were used in an attempt to detect allograft arteriopathy in 79 consecutive orthotopic transplant recipients who were followed prospectively for about 3 years. 7,8 In 30 patients (38%), angiographically significant or autopsy-proven allograft arteriopathy developed. Angiograms were considered positive when 50% luminal narrowing was observed, and autopsy-proven allograft arteriopathy was defined as cross-sectional coronary obstruction $\geq 70\%$.

During follow-up, these patients underwent yearly surveillance echocardiography, gated wall-motion studies at rest and during exercise, thallium scintigraphy with oral dipyridamole "stress," thallium scintigraphy with exercise stress, ambulatory electrocardiographic (ECG) monitoring, and angiographic studies. Positive test results were defined as a decrease in ejection fraction, a wall-motion abnormality, fixed or reversible perfusion defects on thallium scintigraphy, failure of ejection fraction to increase with exercise, lack of systolic blood pressure increase, and ischemic ST changes at maximal exercise (or on ambulatory monitoring).

None of these procedures, however, proved to be a sensitive noninvasive detector of cardiac allograft arteriopathy. All of them had diagnostic sensitivity well below 50%. Specificity, on the other hand, was reasonably good. Exercise testing, ambulatory ECG monitoring, and dipyridamole and exercise thallium scintigraphy had specificities \geq 80%. These tests, when positive, are thus likely to correlate with the presence of obstructive CAD. The best positive predictive value (86%) was noted in patients with an abnormal blood pressure response during supine bicycle exercise. In addition, ambulatory ECG monitoring for arrhythmia, particularly bradycardia, had a positive predictive value of 61%. It should be pointed out here that the prognosis may be very poor for patients with allograft arteriopathy and positive ischemic results on noninvasive studies.9

The diagnostic limitations of noninvasive stud-

ies seem to be related to their use in screening assessment. Further, the diffuse nature of allograft arteriopathy may result in balanced ischemia that is difficult to detect by any imaging method that focuses on differences in regional myocardial perfusion or function. Thus, routine screening arteriography may currently be the best method to detect and follow progression of allograft arteriopathy.^{7,8} In fact, many institutions obtain screening and baseline coronary angiograms within several weeks of heart transplantation because the milieu believed to be conducive to allograft arteriopathy develops soon after the operation. Follow-up angiography can then facilitate identification of incipient vascular abnormalities.²

DISTINCTIVE FEATURES

Symptoms: Because of the diffuse nature of the disease process and the denervation of the cardiac allograft, symptoms related to ischemic heart disease in transplant recipients will be different from those in the general population. Angina, for example, is unusual. Symptoms, such as syncope, are more likely to be related to bradycardia or the development of congestive or low-output heart failure. In addition, the incidence of sudden death may be particularly high in patients with allograft arteriopathy.

Angiographic characteristics: Gao et al5 developed a classification system for diagnosing allograft arteriopathy based on angiographic findings. They stressed the necessity of critically analyzing follow-up arteriograms and comparing them side by side with baseline or prior-year studies. These investigators identified the angiographic hallmark of allograft arteriopathy as an extensive, diffuse, obliterative process that is particularly apparent in distal coronary vessels. Generally, this distal narrowing occurs in secondary branch vessels; welldefined occlusive points are often seen in very distal vessels. Sometimes a distinctive pruned-tree pattern can be noted in cases of the most severe arteriopathy. This pattern of stenosis is distinctly different from that seen in the large epicardial arteries of patients with native CAD.

Many transplant recipients will have proximal epicardial stenoses that are identical to the focal obstructive lesions seen in nontransplant patients with CAD.⁵ Thus, patients with allograft arteriopathy will often have a combination of the typical findings of both arteriopathy and native CAD.

Histologic characteristics: The differences between allograft arteriopathy and native CAD extend to the microscopic level (Table I). Billing-

ham^{10,11} described the histopathology of allograft arteriopathy in detail. Microscopically, the process is a concentric, diffuse proliferation that is marked by hyperplasia of the smooth muscle cells with an accumulation of macrophages, collagen, and ground substance in the endothelial layer. Inflammation of the intimal cells seems to occur first, with subsequent proliferation of smooth muscle cells and macrophages. The movement of smooth muscle cells from the media into the intima appears to occur without disruption of the internal elastic membrane (which is usually noted in native CAD).

A characteristic of allograft arteriopathy is the foam cell, which develops in the intima of the coronary vessels. These cells are the product of phagocytosis of migrating smooth muscle cells and lipid inspissation by the macrophages. Although atheromatous plaques can be found in patients with allograft arteriopathy, they are less likely to calcify and contain a much higher quantity of lipoprotein (particularly low density lipoprotein cholesterol) than do the plagues of native CAD. Plaque rupture with ulceration and thrombus formation can occur, but it is unusual and generally not noted until very late in the disease course. Collagen deposition with intimal scarring and fibrosis can also cause narrowing of the coronary artery lumen; however, cholesterol infiltration with foam cell formation seems to be the major etiologic factor behind luminal compromise.

Some of these histopathologic differences between allograft arteriopathy and native CAD may relate to modern immunosuppressive protocols and, in particular, the use of cyclosporine. Pucci et al¹² suggested that the allograft arteriopathy noted in patients who underwent cardiac transplantation in the pre-cyclosporine era appeared more like the atherosclerosis noted in nontransplant patients. Many of the findings, however, in the pre-cyclosporine era patients resembled those in patients who had been treated with cyclosporine; this suggests that factors other than cyclosporine have a role in the development of allograft arteriopathy.

ETIOLOGY

From a pathophysiologic standpoint, the mechanism responsible for allograft arteriopathy seems to involve 2 primary interrelated conditions: socalled environmental factors, such as hyperlipoproteinemia, hypertension, and persistent nicotine abuse, and immune- or infection-related endothelial injury (Table II).

Environmental risk factors: The more traditional risk factors for CAD may be important, but

TABLE II Risk Factors for Allograft Arteriopathy

Endothelial damage Immunologic activation Viral infection/activation Injury to the organ during harvest

Dyslipidemia

Hypertension Nicotine abuse Obesity

Diabetes Chemotaxis

Platelet aggregation

they have different implications for allograft arteriopathy. Clearly, abnormalities in serum lipoprotein values are apparent in most heart transplant recipients.¹³ Most reports suggest that a significant relation exists between elevated serum cholesterol or triglyceride values and allograft arteriopathy. Arguments for other cardiovascular risk factors, such as hypertension, have been less convincing. Obesity, however, seems to be an extremely important risk factor. 14

Immune-related risk factors: The immunemediated injury hypothesis for allograft arteriopathy is gaining endorsement.^{1,2} Since the disease process is diffuse, and generally limited to the transplanted organ's arteriovascular bed, it is logical to hypothesize that direct endothelial injury occurs in the transplanted heart. Pollock et al15 observed that when there is a human leukocyte antigen mismatch between donor and recipient, substantive allograft arteriopathy is more likely to develop. The existence of circulating cytotoxic antibodies against donor classes 1 and 2 antigens present on the surface of the allograft endothelium also lends support to this hypothesis. 16 Keeping these observations in mind, one might suspect that frequent episodes of rejection requiring special treatment would correlate with development of significant allograft arteriopathy. Indeed, Uretsky et al¹⁷ reported that patients with ≥2 rejection episodes requiring therapy within the first 2 posttransplant years are at increased risk for this disease. Their observation, however, remains controversial.

Other factors related to immunologic activation after transplantation were found to correlate with allograft arteriopathy development. Research at the Multi-Organ Transplant Center demonstrated that the development of new antilymphocyte antibodies after transplantation is associated with new evidence of CAD and diminished survival. 15 Further, the presence of elevated soluble interleukin-2 receptor plasma levels early after transplantation is

TABLE III Possible Interventions for Prevention and Treatment of Allograft Arteriopathy

Intensification of immunotherapy

Blood pressure control

Discontinuation of nicotine use

Dyslipidemia control

Weight optimization

Antiplatelet medication

Anticoagulant therapy

Calcium antagonist therapy

Angioplasty or atherectomy

Bypass surgery

Second transplantation

a predictor of subsequent development of allograft arteriopathy. 18 There are, however, other potential mechanisms for endothelial injury in transplant recipients. These may be related to donor heart procurement and preservation, cyclosporine use, and infection.

Infection-related risk factors: Members of the herpesvirus family have been known to induce a coronary atherosclerosis similar to allograft arteriopathy. Because of the high incidence of cytomegalovirus infection in transplant patients, this virus has received scrutiny as a possible etiologic agent for allograft arteriopathy. 19 Clinical observations suggest that patients with either clinical or subclinical manifestations of cytomegalovirus infection have an increased risk of displaying allograft arteriopathy.²⁰ This contention, however tantalizing, has not yet been proved.21

PREVENTION

We need to focus on understanding the disease process so that allograft arteriopathy can be prevented in the future (Table III). It makes sense, however, to control the traditional risk factors known to be associated with CAD in general, such as hypertension, dyslipidemia, nicotine consumption, and diabetes. Whether intensification of immunotherapy will either prevent the development of allograft arteriopathy or attenuate the process is unknown; clinical trials must address this point.

TREATMENT

Therapy of allograft arteriopathy is still primitive. For focal epicardial lesions, percutaneous transluminal coronary angioplasty (PTCA) has been performed safely, but the restenosis rate after angioplasty may be higher than in native CAD, and its impact on long-term morbidity and mortality is unknown.²² The feasibility of coronary artery bypass surgery has been documented in case reports. Traditional medications that have been used to

inhibit atherosclerosis in general, including antiplatelet compounds (aspirin and dipyridamole), anticoagulants (warfarin and heparin), and fish oil supplements, might prove beneficial.² Schroeder et al²³ made the intriguing observation that development of allograft arteriopathy may be attenuated by therapy with the calcium antagonist diltiazem after transplantation.

Unfortunately, the only definitive therapy for allograft arteriopathy is another heart transplant. In recipients of a second allograft, however, success rates are markedly compromised, with a survival of only 55% at 1 year and 25% at 2 years reported by Gao et al.24

CONCLUSION

A unique form of ischemic heart disease, allograft arteriopathy, is quite different from the obstructive process seen in native CAD. It may well be the primary factor limiting long-term survival after heart transplantation. The etiology of allograft arteriopathy remains problematic. Immunologic factors seem to be most important from a pathophysiologic standpoint, but other agents, such as viral infection, hypertension, and hyperlipoproteinemia, may be exacerbating cofactors. Treatment remains essentially empiric and somewhat primitive. Control of the process may be more successful when the mechanism of cellular proliferation is better defined and the causative factors are identified.

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Abnormal Electrocardiograms and Cardiovascular Risk: **Role of Silent Myocardial Ischemia**

EVIDENCE FROM MRFIT

Jerome D. Cohen, MD

The Multiple Risk Factor Intervention Trial (MRFIT) was designed as a primary prevention study to test the effect of multifactorial intervention on long-term outcome in men with a combination of risk factors that placed them in the top 10-15 percentiles of risk for coronary artery disease. Of the 12,866 patients in this study, the 3,600 men (about 28%) with abnormalities in the baseline electrocardiogram were prospectively identified. They were expected to be at increased risk for coronary events compared with those without electrocardiographic abnormalities. Analysis of cumulative mortality data following antihypertensive regimens that included high dosages of diuretics revealed an association between electrocardiographic abnormalities at rest and diuretic treatment that related to adverse outcome. When the dosages of the diuretic were lowered, this trend was reversed. It is proposed that diuretic-related hypokalemia may predispose patients who may have silent myocardial ischemia to potentially fatal arrhythmias and that use of potassium-sparing antihypertensive regimens be considered in high-risk hypertensive patients. (Am J Cardiol 1992;70:14F-18F)

provocative aspect of silent myocardial ischemia is the wide range of patient Apopulations in which it can be studied. This broad distribution prompts the question: Can results in one patient population have implications for another patient group? This article reports data that suggest that silent myocardial ischemia was a parameter of cardiovascular risk in hypertensive men enrolled in the Multiple Risk Factor Intervention Trial (MRFIT). As will be seen, these data provide insights into risk-factor intervention in other populations.

METHODS

The MRFIT was designed as a primary prevention study to test the effect of multifactorial intervention on long-term outcome in men between the ages of 35 and 57 years whose combination of risk factors placed them at increased risk of coronary artery disease mortality, the primary endpoint of the trial. The risk factors evaluated included hypertension, hypercholesterolemia, and smoking. A total of 12,866 patients were enrolled. Of these, 8,012 patients (approximately 63%) were hypertensive at baseline (hypertension was defined as diastolic blood pressure ≥90 mm Hg and/or taking prescribed antihypertensive medication). At randomization, 4,014 of these had diastolic blood pressure values of 90-99 mm Hg and 1,510 had values ≥ 100 mm Hg; 2,488 were taking antihypertensive medication.

Study subjects were randomized to 1 of 2 groups: the 6,438 members of the first group (usual care [UC] group) were referred to their usual sources of medical care in the community; the 6,428 patients in the second group (special intervention [SI] group) received a more aggressive intervention regimen that consisted of dietary advice to lower cholesterol, counseling to end smoking, and stepped-care antihypertensive drug therapy. The initial dosage administered in a stepped-care

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protocol to the SI group was 50 mg/day of a diuretic, either chlorthalidone or hydrochlorothiazide, increased to 100 mg/day from step 1a to 1b. If diastolic blood pressure goals (range 80–89 mm Hg)¹ were not achieved with this regimen, reserpine and then hydralazine was added to the regimen. The agents used in the initial stepped-care antihypertensive regimen are summarized in Table I.

Inclusion and statistical criteria have been described previously, 1,2 but 2 aspects of the trial design are of particular relevance to this presentation and should be noted. First, all study subjects were asymptomatic and free of clinical coronary artery disease. Since this was a primary prevention trial, all individuals with any indication of existing coronary artery disease (such as a history of angina or myocardial infarction) were excluded. Second, the trial design included an a priori hypothesis that individuals with electrocardiographic (ECG) abnormalities would have a worse outcome than those with normal ECG data when comparing the 2 randomized groups. This hypothesis was based on reasoning that ECG changes may represent subclinical disease and that individuals with ECG findings may be less susceptible to the beneficial effects of risk factor reduction. Accordingly, ECG data were obtained at the second and third screening visits and annually thereafter for 6-7 years.²

RESULTS

Resting ECG abnormalities at baseline were observed in 27.9% of the 12,866 enrollees (Table II). According to Minnesota code classifications, the most prevalent abnormality (11.0%, representing 39.2% of patients with resting ECG abnormalities) was an R wave with an amplitude greater than normal. This abnormality is consistent with underlying hypertensive heart disease or left ventricular hypertrophy. Intraventricular conduction defects (not including bundle branch block) had a prevalence of 6.8%. ST-segment elevation or depression —the latter often a manifestation of myocardial ischemia, especially in high-risk middle-aged men occurred in 3.7% of participants.³ The coronary artery disease mortality data in both subgroups were analyzed versus baseline diastolic blood pressure.

Baseline resting ECG abnormalities absent: At all levels of diastolic blood pressure, the UC group displayed a trend toward higher coronary artery disease mortality, although the trend reached statistical significance only in the group with mild-to-moderate hypertension. Among patients with diastolic blood pressure < 90 mm Hg, the mortality

TABLE I Antihypertensive Stepped-Care Drug Protocol Used in the Multiple Risk Factor Intervention Trial (MRFIT)

Step	Action	Type of Drug	Agent (Dosage)			
1	Initiate	Diuretic	Chlorthalidone (50–100 mg/day)*			
			Hydrochlorothiazide (50–100 mg/day)			
2	Add	Antiadrenergic	Reserpine (0.10-0.25 mg/day)			
			or			
			Methyldopa† (500-2,000 mg/day)			
			or			
			Propranolol† (80–480 mg/day)			
3	Add	Vasodilator	Hydralazine (30–200 mg/day)			
4	Add	Antiadrenergic	Guanethidine (10–200 mg/day)			
*Subsequently changed to chlorthalidone ≤ 50 mg/day. †Alternative if reserpine contraindicated or not tolerated.						

TABLE II Distribution of Resting Electrocardiographic Abnormalities* and Mean Diastolic Blood Pressure at Entry into the Multiple Risk Factor Intervention Trial (MRFIT)

	Partici	pants	Those with	Baseline	
Type of Abnormality (MC)	No.	% of All	Abnormalities (%)		
High R waves (3.1–3.3)	1,410	11.0	39.2	93.5	
IV conduction defects (7.1–7.8)	869	6.8	24.1	90.1	
Negative T waves (5.1–5.3)	511	4.0	14.2	94.7	
Arrhythmias (8.1–8.6)	490	3.8	13.6	91.5	
Left-axis deviation <−30°	380	3.0	10.6	92.6	
ST elevation (9.2)	240	1.9	6.7	90.4	
ST depression (4.1–4.3)	236	1.8	6.6	95.1	
Q-QS waves (1.1-1.3)	184	1.4	5.1	92.3	
AV conduction defects (6.1–6.8)	180	1.4	5.0	89.8	
Right-axis deviation ≥ 120°	17	0.1	0.5	91.4	
Low QRS amplitude (9.1)	6	0.0	0.2	85.7	
Any abnormality	3,593	27.9	100.0	92.0	
No abnormality	9,272	72.1	-	90.5	

*Because the abnormalities are not mutually exclusive, participants may be counted more than once.

AV = atrioventricular; BP = blood pressure; IV = intraventricular; MC = Minnesota code.

code. From Am J Cardiol.³

rate was 2.7% (number of deaths = 49) in the SI group compared with 3.2% (n = 59) in the UC group (p = 0.20). Among participants with diastolic blood pressure of 90–99 mm Hg, the rates were 2.2% (n = 32) in the SI group compared with 3.3% (n = 49) in the UC group (p = 0.04). Among participants with diastolic blood pressure \geq 100 mm Hg, the rates were 3.2% (n = 16) in the SI group compared with 4.6% (n = 23) in the UC group (p = 0.13).

Baseline resting ECG abnormalities present:

This group displayed an opposite trend in coronary artery disease mortality with the exception of patients who had moderate to severe hypertension (diastolic blood pressure ≥ 100 mm Hg). Among participants who were normotensive at baseline

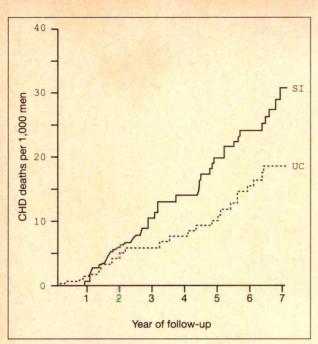


FIGURE 1. Cumulative coronary artery disease (CHD) mortallty for hypertensive men with baseline electrocardiographic abnormalities at rest in the Multiple Risk Factor Intervention Trial. A total of 3,593 men in the special intervention (SI) and usual care (UC) groups—almost 30% of all -showed such abnormalities. (Adapted from Am J Cardiol.3)

(diastolic blood pressure < 90 mm Hg), the coronary artery disease mortality rate was 3.7% (n = 22) in the SI group compared with 2.6% (n = 15) in the UC group (p = 0.15). Among participants with diastolic blood pressure of 90-99 mm Hg, the increased coronary artery disease mortality rate in the SI group reached statistical significance at 4.3% (n = 24) versus 2.2% (n = 12) in the UC group (p = 0.03). By contrast, among patients with diastolic blood pressure ≥100 mm Hg, the SI group tended to have a better outcome, with a mortality rate of 4.5% (n = 12) versus 7.2%(n = 17) in the UC group (p = 0.14).

The 7-year cumulative coronary artery disease mortality data for hypertensive participants with an abnormal resting ECG are summarized in Figure 1.3 Although coronary artery disease mortality was 29.2 per 1,000 in the SI group versus 17.7 per 1,000 in the UC group, the difference was not quite statistically significant (p = 0.06).

Within-group analysis revealed a relation between ECG abnormalities at rest and diuretic treatment.³ Among SI men with baseline ECG abnormalities, those receiving diuretics were at 3.34-fold greater risk of death from coronary artery disease than those not receiving diuretics. (The excessive mortality rate mainly reflected cases of sudden death, defined as death within 60 minutes.) Among SI participants with a normal resting ECG,

the corresponding risk was 0.95. Although some patients in the UC group were also given the diuretics by their own physicians, the doses they received on average were lower, and no correlation between diuretic use and coronary artery disease mortality was found. These data prompted a reevaluation of the diuretic regimen used in MRFIT, and 2 years before the trial ended SI participants taking hydrochlorothiazide were switched to chlorthalidone at a maximum daily dosage of 50 mg.4

The difference between the mortality rates of SI and UC participants observed before and after this change in regimen was consistent with the hypothesis that hydrochlorothiazide at the higher doses contributed to the higher coronary artery disease mortality.4 Before the regimen change, the coronary artery disease mortality rate was 44% higher for SI patients than for UC patients in those clinics predominantly using hydrochlorothiazide for antihypertensive treatment (p = 0.23). After the regimen change, the coronary artery disease mortality rate for SI patients was 28% lower than for UC in those same clinics (p = 0.14). At 10.5 years of follow-up, the mortality rate for coronary artery disease in the SI group was 15% lower (p = 0.19) than in the UC group and 11% lower (p = 0.13) for all causes of death combined.4 These data are for all participants, including those with and without baseline resting ECG abnormalities.

DISCUSSION

Among MRFIT participants with baseline ECG abnormalities, it is reasonable to assume that, in at least some of these individuals, this represents asymptomatic or silent myocardial ischemia. Positron emission tomographic (PET) studies have shown that physical exercise, mental stress, cold temperatures, and a wide range of other physiologic stimuli can provoke episodes of silent myocardial ischemia in susceptible individuals.⁵ In a study using radionuclide ventriculography, public speaking—an anxiety-provoking, personally meaningful task—induced a level of cardiac dysfunction similar to that produced by exercise testing.⁵ Two factors indicate that ischemia was the cause of the segmental wall-motion abnormalities induced by mental stress: (1) the correlation between these abnormalities and thallium perfusion defects and (2) their occurrence within the distribution of documented coronary artery disease.5

Catecholamine effects, such as increased myocardial oxygen demand, have been proposed as a possible mechanism for stress-induced silent myocardial ischemia.⁵ Other investigators have reported data suggesting that endothelial dysfunction may occur early in the coronary disease process and that this dysfunction may result in paradoxical vasoconstriction of the coronary arteries under stress.6

In patients with confirmed coronary artery disease, the prognostic importance of silent myocardial ischemia has been convincingly established. These patients with coronary artery disease and silent myocardial ischemia are at high risk for subsequent cardiac events.⁷⁻⁹ In asymptomatic, high-risk men with resting ECG abnormalities, these data suggest that the high-dose diuretic regimen may have interacted to precipitate an adverse effect on outcome. Particularly at high doses, thiazide diuretics are associated with hypokalemia and hypomagnesemia; these electrolyte abnormalities can place patients at risk for ventricular arrhythmias.^{2,10-12} The release of catecholamines (such as epinephrine) during excessive sympathetic activity, as might occur during periods of stress, may also induce hypokalemia¹³ and potentiate the effect of diuretic-related potassium loss. 14 Ventricular ectopic activity that can result from hypokalemia may then cause sudden death in a predisposed high-risk individual.¹¹

Low-dose chlorthalidone treatment has been evaluated more recently in the setting of a different population, and the favorable outcome is consistent with the observations from MRFIT. The Systolic Hypertension in the Elderly Program (SHEP) was conducted in an elderly population (aged ≥ 60 years) with isolated systolic hypertension. 15 In this study, 61.3% (n = 2,365) of the active treatment group and 60.7% (n = 2,371) of the placebo control group had baseline resting ECG abnormalities. By study end, 46% of the participants in the active treatment group were receiving a low-dose diuretic—12.5 or 25 mg of chlorthalidone—daily. Among participants with baseline abnormalities, 29 sudden deaths occurred in the active treatment group compared with 36 in the placebo group, and the relative risk of nonfatal myocardial infarction plus coronary death was 0.69 (95% confidence interval, 0.50–0.94). Among participants without ECG abnormalities, the active treatment group had 15 sudden deaths compared with 10 in the placebo group (relative risk 0.83; 95% confidence interval, 0.53–1.29). Importantly, treatment of hypertension with low-dose chlorthalidone reduced total stroke incidence by 36% over a 5-year period when comparing the active treatment group to the placebo control group. The SHEP investigators concluded that these data suggest a

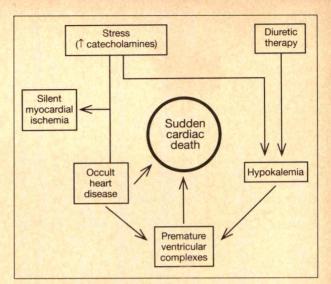


FIGURE 2. Proposed relation between silent myocardial ischemia, diuretic use, and sudden cardiac death. ↑ = increase.

benefit for treatment of patients with isolated systolic hypertension, including those with and those without baseline ECG abnormalities.

In light of these data, it seems reasonable to speculate that premature ventricular complexes may play a central role in the interaction between occult heart disease and the effects of high-dose diuretic therapy (Figure 2). Hypertensive patients who have occult heart disease may experience episodes of silent myocardial ischemia during physical or mental stress. Diuretics administered in high doses to manage hypertension in these patients can provoke hypokalemia. The combination of ischemia and potassium deficiency creates a favorable environment for ventricular arrhythmias, which in the milieu of occult heart disease, may trigger tachyarrhythmia and sudden death. The benefits of low-dose diuretics for hypertensive treatment have been clearly established. With further advances in our understanding of how silent myocardial ischemia and hypokalemia may interact, it is hoped that the benefits of lowering blood pressure in high-risk hypertensive patients can be further advanced.

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Role of Myocardial Oxygen Demand in the Pathogenesis of Silent Ischemia During Daily Life

Prakash C. Deedwania, MD. Enrique V. Carbajal, MD.

The role of myocardial oxygen demand in the pathogenesis of silent ambulatory myocardial ischemia was evaluated by reviewing and assessing the methods and results of recent studies. The performance of simultaneous ambulatory electrocardiographic and blood pressure monitoring in 25 men with proven coronary artery disease (CAD) revealed significant increases in heart rate and blood pressure (p < 0.001) preceding most silent ischemic events. By plotting the mean heart rate obtained at 5-minute intervals during the 30 minutes before an ischemic event, the ischemic heart rate was shown to be significantly higher (95 \pm 15 vs 74 \pm 11 beats per minute [bpm]; p < 0.01) than the nonischemic heart rate. The evaluation of heart rate changes during ambulatory ischemia (in patients with CAD and ischemia induced by an exercise test using gradual work load increments) showed a significant heart rate increase (>10 bpm) at 1-5 minutes preceding the onset of ST-segment depression. Heart rate increases during exercise testing according to the gradual work load increments of the National Institutes of Health protocol were compared with the heart rate preceding ischemic events during daily life monitored by ambulatory electrocardiography and were found to be closely related. In contrast, heart rate increases that occurred during exercise testing using the standard Bruce protocol were higher and correlated less with those preceding ischemia in daily life. Heart rate and blood pressure increased significantly in most silent ischemic episodes, indicating that increased myocardial oxygen demand plays a significant role in the pathogenesis of myocardial ischemia during daily life.

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ccording to the results of ambulatory electrocardiographic monitoring (AEM) stud-Lies, patients with coronary artery disease (CAD) frequently experience transient myocardial ischemic episodes during routine daily activities.¹⁻⁴ The vast majority of these episodes are asymptomatic; they usually occur during minimal physical activity or at rest. Although most of the patients evaluated in these studies displayed evidence of fixed atherosclerotic CAD and ischemia during exercise testing, the role of increased myocardial oxygen demand in the genesis of ischemic episodes during daily life remains controversial.

Because most ischemic episodes occur at rest or during minimal physical activity, it has been suggested that an increase in myocardial oxygen demand might not play a significant role in spontaneous ischemia during daily life. 1,5,6 Further, relatively small heart rate increases preceding transient ischemic episodes recorded during AEM⁶⁻⁸ suggest that other pathogenetic mechanisms, such as coronary vasospasm or increased platelet aggregation, may play dominant roles. This hypothesis is supported by the indirect evidence derived from comparing the heart rate increase before onset of ischemia during exercise testing with that observed during AEM.8

Because the heart rate increment during spontaneous ischemic episodes was less than that observed during exercise-induced ischemia, it has been proposed that transient reductions in coronary blood flow may play a major role in the genesis of silent ambulatory myocardial ischemia.⁶ However, the results of these studies are conflicting and inconclusive. For example, Deanfield et al⁶ found that only 34% of transient ischemic events were preceded by a heart rate increase of > 10 beats per minute (bpm). In a later report, Chierchia et al⁸ found that 42% of silent ischemic events followed a heart rate increment of ≥ 5 bpm during the 15 minutes before onset of significant ST-segment depression. In contrast to these reports, more

TABLE | Heart Rate, Systolic Blood Pressure, and Double Product During Ambulatory Monitoring at Baseline. Before Onset of ST Depression, and at 1-mm and Peak ST Depression

		Base	line		Defere	Onast	۸+ 1 .		A+ Do	ak
	Awake		Sleep		Before Onset of ST Depression		At 1-mm ST Depression		At Peak ST Depression	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Heart rate	72.8	12.7	58.9	8.0	75.2*	16.6	91.7*	19.4	99.6*	19.9
Δ Heart rate	_		_	_	5.3	11.3	21.8	13.1	30.4	13.6
Systolic BP	121.2	14.9	110.6	15.4	130.2*	18.5	137.5*	22.5	141.7*	21.5
Δ Systolic BP		_	_		9.8	18.9	18.0	21.9	22.1	22.5
Double product	8,818	1,885	6,522	1,289	9,486*	2,504	12,400*	2,981	13,792*	3,329
Δ Double product		The same	- 16	_	1,262	2,031	4,194	2,300	5,627	2,760

*p < 0.001 compared with baseline. Δ = change; double product = heart rate × systolic blood pressure; ST = ST segment. Reprinted with permission from *Circulation*. ¹¹

recent studies have shown that most transient ischemic episodes, both silent and symptomatic, are preceded by a significant increase in heart rate.9-13 Quyyumi and colleagues9 demonstrated that >96% of transient ischemic events were preceded by an increase in heart rate. Similarly, Hausmann et al¹⁰ showed a heart rate increase of > 10 bpm before 95% of silent ischemic episodes during ambulatory monitoring.

As a result of these conflicting reports, the precise mechanism of myocardial ischemia during daily activity remains unclear. Further, these studies did not simultaneously evaluate blood pressure, an important determinant of myocardial oxygen demand. The primary purpose of this article is to evaluate the available evidence supporting the role of myocardial oxygen demand by reviewing the results of recent studies that have addressed the pathogenesis of silent myocardial ischemia during daily life.

COMPREHENSIVE MONITORING OF **HEMODYNAMIC ISCHEMIC CHANGES**

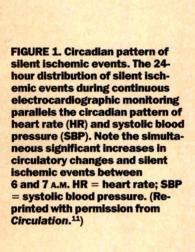
Although some earlier studies simultaneously evaluated blood pressure and electrocardiographic (ECG) changes, most were conducted in hospitalized patients with angina pectoris. 14-16 Since these studies evaluated the circulatory changes that occurred after the onset of primarily symptomatic ischemic events, they provided no information about the changes in blood pressure that precede the onset of silent ischemic episodes. Therefore, we recently performed simultaneous AEM and blood pressure monitoring in an effort to elucidate the pathophysiologic mechanism responsible for engendering silent ischemic events.11

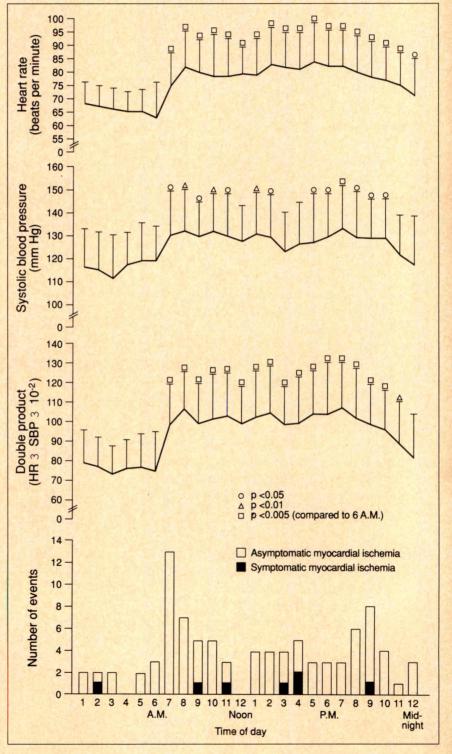
To this end, we evaluated the changes in heart rate and blood pressure that preceded the onset of silent myocardial ischemia in 25 men (mean age 61

years) with stable angina and documented CAD.11 Patients were instructed to pursue their usual daily activities while maintaining a precise record of anginal episodes and nitroglycerin use during the monitoring period. The diagnostic criteria for ischemic events on AEM were horizontal or downsloping ST-segment depression ≥ 1 mm persisting for 80 msec after the J-point and lasting for ≥ 1 minute. Those episodes meeting the diagnostic criteria were classified as symptomatic or silent on the basis of patients' diary entries. Baseline heart rate and blood pressure values were calculated separately during sleep and wakefulness by averaging all available values recorded during a 2-hour ischemia-free period. These baseline heart rate values were then compared with the values taken 1 minute before the recording of 1 mm of STsegment depression and at peak ST-segment depression during each ischemic event. Similarly, the baseline systolic blood pressure values were compared to those obtained within 10 minutes preceding the ischemic event, at 1 mm of ST-segment depression and at peak ST-segment shifts. All patients showed evidence of exercise-induced ischemia during maximal exercise tolerance testing. During exercise, the heart rate and systolic blood pressure at baseline, 1 mm of ST depression, peak exercise, and maximum ST depression were obtained and compared with the corresponding values recorded during AEM.

During 650 hours of monitoring, 92 transient ischemic episodes meeting the diagnostic criteria were observed. Of these, 85 episodes (92%) were silent. When compared with baseline values, both heart rate and systolic blood pressure showed significant increases before silent ischemic episodes (Table I). Of the 85 silent ischemic episodes, 61% were preceded by a significant increase (average ≥ 5 bpm) in heart rate. Systolic blood pressure, measured an average of 6 minutes before the episodes, also increased significantly in 73% of the 56 events with available blood pressure data. As expected, greater increases in both heart rate and systolic blood pressure took place at 1 mm of ST-segment depression and at peak depression.

Hemodynamic changes during exerciseinduced versus ambulatory ischemia: When the percentages of heart rate and blood pressure changes from baseline during exercise testing were compared with those observed during AEM, significant differences were revealed only in the heart rate and double product noted at 1 mm of ST-segment depression. Interestingly, despite the greater degree of ST-segment depression found during exercise testing (2.2 \pm 1.1 vs 1.5 \pm 0.6 mm during AEM; p <0.001), no significant differences between the percentage increases in heart rate and





blood pressure were seen at peak ST-segment depression.

Circadian pattern of silent ischemic events:

The 24-hour distribution of the 92 transient ischemic events, as well as changes in heart rate, systolic blood pressure, and double-product values, revealed a circadian pattern (Figure 1). The total number of silent ischemic events abruptly increased during the morning hours, with 34% occurring between 6 A.M. and noon. The heart rate, systolic blood pressure, and double product paralleled the silent ischemic activity with simultaneous abrupt increases during these hours. Silent ischemic episodes peaked again between 8 and 9 P.M. This distribution of silent ischemic events was similar to the circadian pattern of circulatory changes during 24-hour monitoring.

Study results: In patients with stable CAD, most silent ischemic events during unrestricted daily activity were preceded by increases in heart rate and systolic blood pressure. Further, the progressive increase in circulatory changes during ischemic episodes, whether silent or symptomatic, provided good evidence of the hemodynamic consequences associated with myocardial ischemia. These hemodynamic changes might even intensify and lengthen the duration of ischemia.

The net changes in heart rate and systolic blood pressure during the silent ischemic events recorded on AEM showed significant increases from corresponding baseline values; however, these changes were not as great as those observed with exercise testing. The relative percent increases in systolic blood pressure at 1 mm of ST-segment depression during exercise testing and AEM were comparable. The similarities between circulatory changes during exercise-induced ischemia and silent ambulatory ischemia further support the concept that increased myocardial oxygen demand plays a significant role in the genesis of silent myocardial ischemia during daily life.

CORROBORATING INVESTIGATIONS

Several other recent studies that evaluated the role of heart rate changes in the pathogenesis of transient ischemia during AEM have confirmed the above findings by showing that a significant increase in the heart rate precedes the vast majority of ischemic episodes. McLenachan et al¹² studied the role of heart rate changes before the onset of ischemia during AEM in 21 patients by plotting mean heart rate obtained at 5-minute intervals during the 30 minutes preceding an ischemic event. Significant increases in heart rate preceded most ischemic episodes. The heart rate began to increase at approximately 30 minutes before the onset of ischemia and the increment became significant at 15 minutes before onset of ST-segment depression. When mean heart rates during the nonischemic period were compared, the ischemic heart rate was significantly higher (95 \pm 15 bpm vs 74 ± 11 bpm, p < 0.01) than the nonischemic heart rate. Although the heart rate increased frequently during the monitoring period, the duration of heart rate increases preceding ischemic events was significantly longer than those unassociated with ischemic episodes (median 35 minutes vs 7.5 minutes, p < 0.001). These results suggest that in some cases, a persistent increase in heart rate may be needed to trigger ischemic events.

The pathogenetic significance of heart rate changes was also evaluated by observing the effects of therapy with propranolol or nitroglycerin on ischemic episodes during AEM.¹² Treatment with propranolol more effectively suppressed ischemic episodes that demonstrated high heart rates (> 100 bpm) at their onset, suggesting that the beneficial effect of this drug resulted from its reduction of myocardial oxygen demand (Figure 2). In contrast, nitroglycerin more effectively suppressed ischemic events accompanied by low heart rates (<80 bpm) at their onset, indicating that these episodes might result primarily from alterations in coronary blood flow.

The role of increased myocardial oxygen demand in relation to ischemia during daily life was further evaluated in a study of 50 patients with CAD and exercise-induced ischemic ST depression. 13 All patients had experienced ischemia during a symptom-limited bicycle exercise test that included gradual increments in work load. Ischemic ST-segment depression was observed during AEM in 62% (n = 31) of patients. Most events (94%) were silent; only 14 events (6%) were associated with angina. In 47% of ischemic episodes, the heart rate increased significantly (>10 bpm) and the increase persisted for >5 minutes before the onset of ischemia. In an additional 35% of episodes, the heart rate increase occurred 1-5 minutes before the onset of ST depression. The ST-segment depression preceded the increase in heart rate in only 8% of episodes. Although 35% of ischemic episodes occurred between 6 A.M. and noon, no significant diurnal variation in heart rate was associated with ischemic ST-segment depression.

Interestingly, a significant relation was found in this study between heart rate at the onset of exercise-induced ischemia and at the onset of ischemic episodes during AEM (r = 0.74, p < 0.001) in most patients. ¹³ Those patients who had a high threshold for exercise-induced ischemia exhibited episodes of ischemia during AEM that were associated with high heart rates. This relation was demonstrated by using a supine bicycle exercise protocol that produced gradual increases in work load to simulate the work load levels attained during routine daily activities.

The significance of gradually increasing work load during exercise testing to compare the magnitude of heart rate changes during exercise-induced ischemia with those observed during ischemic episodes on AEM was recently emphasized by Panza et al.¹⁷ In this study, 70 patients with stable CAD had 48-hour AEM and underwent exercise treadmill testing using 2 different exercise protocols

(National Institutes of Health [NIH] combined and Bruce protocols). The mean heart rate at onset of exercise-induced ischemia correlated better with the number of ischemic episodes detected during AEM when the NIH protocol was used than when the Bruce protocol was used. These results, like the findings of Hinderliter et al,13 showed that heart rate at onset of ischemic episodes during daily life is not significantly different from heart rate at onset of ischemia during progressive increases in work load with the NIH protocol (Figure 3). In contrast, the relation between heart rates at the onset of ischemia during the Bruce protocol and during AEM was not as strong. The Bruce protocol was associated with steeper increases in heart rate, higher mean heart rate, and a shorter time before onset of ischemia.

The results of both latter studies^{13,17} provide a

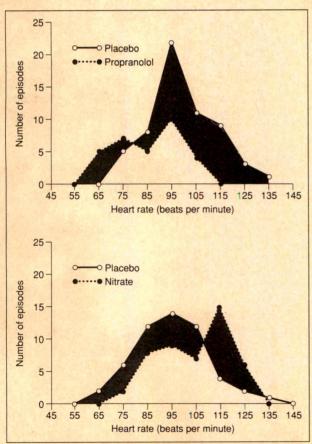


FIGURE 2. Heart rate values at onset of ischemia for 59 episodes during treatment with placebo and 31 episodes during treatment with propranolol (top), and for 53 ischemic episodes detected during placebo treatment and 47 during nitroglycerin treatment (bottom). Top: Shaded areas represent the reduction in ischemic events at high heart rates and the small increase in events at lower heart rates with propranolol therapy. Bottom: Shaded areas represent the reduction in ischemic events at low heart rates and the increase in events at higher heart rates during nitrate therapy. (Reprinted with permission from Circulation. 12)

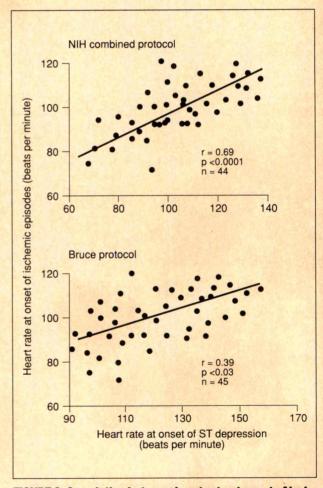


FIGURE 3. Correlation between heart rate at onset of ischemic episodes during ambulatory electrocardiographic monitoring (AEM) and heart rate at onset of ST-segment depression during exercise testing with the National Institutes of Health (NIH) combined protocol (top) and the Bruce protocol (bottom). Both exercise protocols correlated with AEM; however, the correlation with the NIH combined protocol was significantly stronger. (Reprinted with permission from J Am Coll Cardiol. 17)

reasonable explanation for the previously reported lack of relation between heart rates at the onset of exercise-induced ischemia and AEM-recorded ischemia. Most earlier studies used the standard Bruce protocol, in which rapid increments in work load are imposed during exercise testing. Therefore, it is not surprising that the heart rates at the onset of exercise-induced ischemia in previous studies were significantly greater than those that occur during daily life.

CLINICAL IMPLICATIONS

This review of the available data clearly demonstrates that, as in anginal episodes, most silent ischemic episodes are preceded by significant increases in heart rate and/or systolic blood pressure. Thus, an increase in myocardial oxygen demand must play a significant role in the genesis of silent ischemic episodes. These data are clinically important, since the appropriate choice of therapy should be based on the underlying pathophysiologic process. If increased myocardial oxygen demand (evidenced by increased heart rate and blood pressure responses preceding silent ischemic events) plays a significant role, the ideal therapeutic choices are drugs such as β-blocking agents or calcium antagonists, which slow the heart rate and reduce blood pressure. 18-20

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Use of Intracoronary Ultrasonography in Assessing Pharmacotherapy for Myocardial Ischemia

Morton J. Kern, MD

Intracoronary ultrasonography can provide morphologic and physiologic information on coronary vasomotor responses to pharmacotherapy. Preliminary studies indicate a high correlation between dimensions determined by 2-dimensional echocardiography, angiography, and pathology. Similarly, the emerging data on intracoronary Doppler flow velocity responses beyond atherosclerotic obstructions before, during, and after coronary balloon occlusion will provide further insights into myocardial oxygen supply and its responses to pharmacotherapy during controlled myocardial ischemia.

(Am J Cardiol 1992;70:25F-34F)

harmacologic modulation of myocardial ischemia has been studied during balloon occlusion of the coronary arteries in patients undergoing percutaneous transluminal coronary angioplasty. In this procedure, measurement of left ventricular function was achieved simultaneously by traditional hemodynamic methods and by transthoracic 2-dimensional (2D) and Doppler echocardiographic techniques.¹⁻⁴ With the controlled model of mechanically induced myocardial ischemia, the use of various pharmacologic agents (e.g., calcium antagonists, β blockers, nitrates, and perfluorocarbon oxygenated solutions) can be evaluated for the degree of amelioration of myocardial ischemia that each drug may produce during transient cessation of coronary blood flow.^{5,6}

In addition to providing precise measurements of coronary artery dimensions with 2D imaging, intracoronary ultrasonography can gauge responses to coronary vasomotor activity (i.e., vasodilation and vasoconstriction).^{7,8} Further, intracoronary Doppler ultrasonography can accurately measure coronary blood flow velocity. 9,10 Because of its ability to determine the morphologic and physiologic effects of mechanical and pharmacologic perturbations, intracoronary ultrasonography has great potential for revealing alterations in cardiac physiology at rest and during therapeutic interventions. Future advances combining these 2 ultrasonographic methodologies will likely provide data on volumetric flow responses, information critical in the assessment of myocardial oxygen supply during ischemia, and the response of myocardial ischemia to pharmacotherapy.

INTRAVASCULAR ULTRASONOGRAPHY

Intravascular ultrasonographic technology now permits positioning of a 20–40 MHz piezoelectric silicon crystal either on a rotating internal cable or mounted externally and electronically controlled on a 3.5–5.0 French (F) angioplasty-style catheter. These imaging systems provide sufficient 2-D

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image quality to allow interpretation of the transverse structural composition of a coronary artery in a plane perpendicular to the catheter long axis (Figure 1). Imaging of the muscular arteries, such as those of the human coronary system, discloses a 3-layered structure with characteristic, distinctive reference features, permitting definition of the outer boundary of plaque and the inner luminal area.

Studies of intravascular ultrasonographic images indicate satisfactory correlation with histopathologic vessel structure. 11,12 Although correlations of luminal diameter and wall thickness with histologic measurements have been uniformly high, measurements of the dimensions of vessel wall layers and overall wall thickness are reported to be less accurate than determinations of luminal diameter. 8 St. Goar et al 13 used intravascular ultrasonography to image angiographically normal coronary arteries and provide an in vivo comparison with quantitative angiography. After introducing a 30 MHz ultrasonographic catheter into the mid-left anterior descending artery via the left main coronary ostium, these researchers performed simultaneous measurements at 76 sites. Coronary diameters determined angiographically correlated closely with diameters measured ultrasonographically (r = 0.86-0.88), depending on the perpendicular alignment of the intravascular catheter.

The rendering of layers of the muscular artery in the ultrasonographic image is further complicated by variations in the acoustic properties of the tissue being imaged. The luminal, intimal, medial, and adventitial interfaces have relatively large differences in acoustic impedance that provide surfaces for differentiation. However, there is a trailingedge effect of echocardiographic imaging that causes spreading or "blooming" of the intimal image, which results in more widely spaced boundaries for the intima than those determined by histologic and pathologic examination.8 In vivo intracoronary ultrasonographic measurements closely correlate with those obtained by quantitative angiography¹³; however, the former tend to be slightly larger.

Although several systems provide high-quality images in vivo during cardiac catheterization of patients, visualization of the arterial wall architecture with ultrasonography has a distinct practical advantage over fiberoptic angioscopy, which requires arterial occlusion and flushing with a clear solution. In addition to wall thickness, intravascular ultrasonography reveals subintimal details of atheroma. After establishing reference values for

these features, the dimensions of the entire vessel and intraluminal area can then be computed. Extrapolation of 3-dimensional images of vessels from the 2-D slices is a reasonably straightforward extension of current computer technology; the result provides a topographic map of regions that may respond favorably to pharmacotherapy and regions that may respond in an abnormal fashion.¹⁴

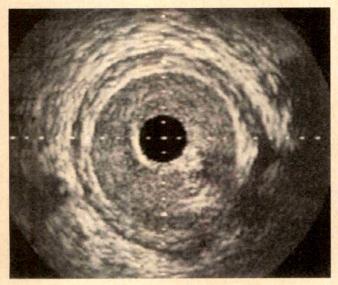
An alternative to direct intracoronary imaging involves use of the transvenous route, i.e., the catheter is introduced into the anterior intracardiac vein via the coronary sinus. 15 Sudhir et al 16 inserted 5 F, 30 MHz imaging catheters into the coronary venous system of 11 human subjects undergoing right heart catheterization in which the left anterior descending coronary artery could be easily identified. Angiographic correlations and differentiation of the left anterior descending and circumflex coronary arteries could be obtained in most patients.

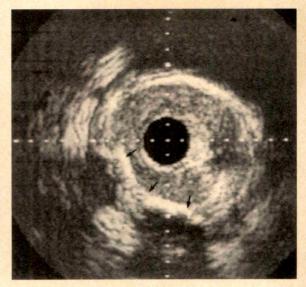
Recently, researchers have coupled an intravascular ultrasound transducer with an angioplasty balloon catheter. 17,18 The ultrasound transducer, positioned within the angioplasty balloon, can obtain quantitative and qualitative data on lumenplaque-vessel wall interactions and alterations preceding, during, and after coronary or peripheral angioplasty in patients. Such techniques may have implications in the selection of interventional devices as well as in determining the vasomotor response of abnormal vessels to various common drugs after angioplasty trauma.

INTRACORONARY DOPPLER **ULTRASONOGRAPHY**

Doppler catheters: Several intracoronary Doppler catheters are currently available. The nonsubselective, Judkins-style, 8 F coronary Doppler catheter (Cordis Corporation; Miami, FL) is a standard diagnostic Judkins-shaped angiographic catheter with a 20 MHz crystal embedded in the tip. With this device, left main coronary blood flow velocity can be easily measured in most patients. No deep instrumentation of the coronary artery is performed. The nonselective coronary catheter, the accuracy of which has been validated against subselective catheter measurements, is used in patients with syndrome X, cardiac transplantation, valvular heart disease, or cardiomyopathy who do not have more distal coronary atherosclerosis. When compared to subselective measurements, proximal flow velocity responses are nearly equivalent to those in more distal locations. 19

Subselective coronary catheters are 3 F size,





Mid-LAD Proximal LAD

FIGURE 1. Two-dimensional intracoronary ultrasound images obtained with a 30 MHz mechanical transducer in the proximal and mid-left anterior descending coronary artery (LAD). The division markers (0.5 mm) are used to quantitate changes in dimension during various interventions. The dimensions of the vessel diminish more distally, and the irregularity on the inferior aspect (6–9 o'clock arrows) of the mid-LAD section demonstrates atherosclerotic plaque. Vasomotion and responses to pharmacotherapy can be accurately measured.

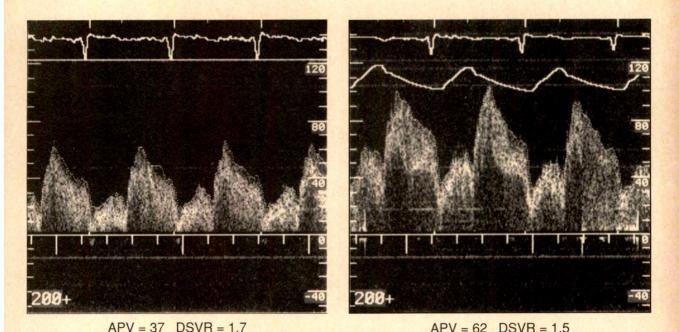
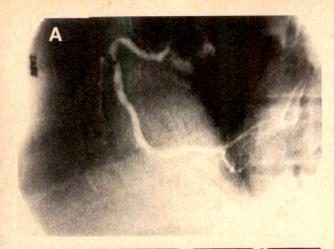
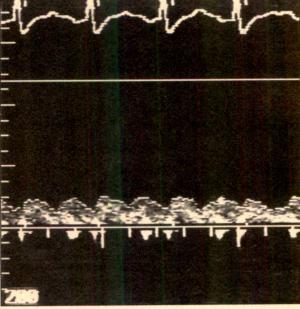
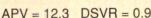
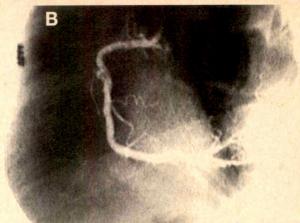


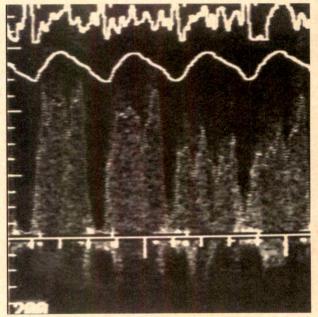
FIGURE 2. Doppler flow velocity signals at baseline (left) and during adenosine-induced hyperemia (right). The smaller systolic flow integral (gray area) begins immediately after the R wave and the larger diastolic flow velocity integral begins at the aortic pressure dicrotic notch. The peak diastolic velocity and average peak velocity (APV) demonstrate a near doubling with coronary hyperemia. Velocity scale is 0-200 cm/sec. DSVR = diastolic/systolic velocity ratio.









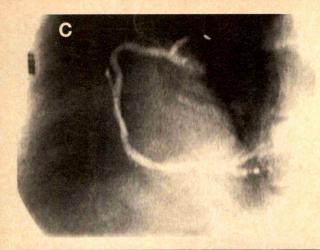


APV = 41.0 DSVR = 0.7

similar to angioplasty-style balloon catheters, and are inserted using standard coronary angioplasty technique with 8 F guiding catheters and 0.014inch guide wires. Coronary flow velocity can be measured using a zero cross technique within the large epicardial coronary branches; the subselective 3 F Doppler catheters (Millar Instruments; Houston, TX) are not generally used to cross coronary atherosclerotic lesions.

Because of its small size, the Doppler-tipped guide wire (0.018-inch Flowire, Cardiometrics, Inc; Mountain View, CA) is the only tool that can provide information both proximal and distal to coronary stenoses in patients with or without coronary artery disease. In addition, the Doppler guide wire provides enhanced data by employing spectral velocity signal analysis.

Determining blood flow velocity: Intravascular catheters and guide wires equipped with miniaturized echocardiographic crystals for Doppler flow measurements also provide the means for assessing physiologic responses to mechanical and pharmacologic coronary manipulations. Coronary vasodilative reserve can be determined by assessing coronary blood flow velocity augmentation with a variety of agents, such as nitroglycerin, papaverine, adenosine and contrast media.9 The recent development of the 0.018-inch, 12 MHz, Doppler-tipped angioplasty-style guide wire has introduced a technique to measure not only proximal, but also, for the first time, distal coronary flow velocity; this capability will allow assessment of the physiologic significance of intracoronary obstructions and the vascular responses to pharmacologic therapy.20,21 In addition, the Doppler-tipped guide wire can be used during angioplasty to assess collateral flow (determined by flow velocity reversal)22,23 as well as the influence of diastolic pressure augmentation on



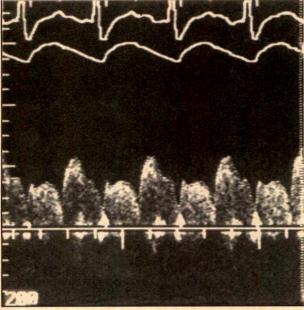


FIGURE 3. A: Angiogram (top) demonstrating proximal 95% stenosis and corresponding flow velocity (bottom). Velocity scale is 0-200 cm/sec. Note abnormal flow velocity pattern compared with Figure 2. B: After initial dilation, angiogram has hazy appearance at lesion site. Flow veloctty shows high-velocity jet (100 cm/sec) that corre sponded to 30 mm Hg residual lesion gradient. C: After final dilations, angiogram appears nearly normal, with an increase in the distal flow velocity and restoration of the normal diastolic-predominant pattern. APV = average peak velocity: DSVR = diastolic/systolic velocity ratio.

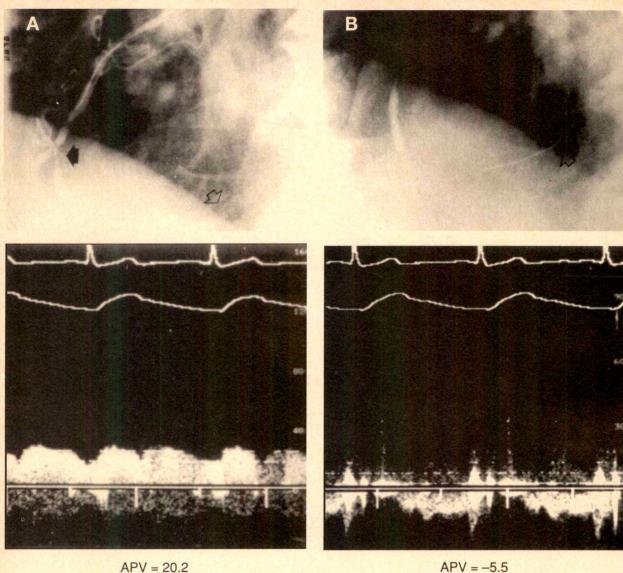
distal coronary flow velocity during intraaortic balloon pumping.^{24,25}

APV = 29.2 DSVR = 1.2

Assessing pharmacologic hyperemia and coronary flow reserve: Intracoronary Doppler catheters can measure maximal and submaximal changes in coronary flow velocity in response to a variety of coronary vasodilators. Coronary hyperemia is commonly produced by administration of intracoronary or intravenous adenosine or use of intracoronary papaverine, nitroglycerin, or contrast media. The typical coronary hyperemic response observed with the Doppler guide wire illustrates the characteristic systolic and diastolic components of coronary flow velocity (Figure 2). After intracoronary administration of 12 µg of adenosine, baseline peak diastolic flow velocity increased from 65 to 105 cm/sec (Figure 2). The area inscribed by the diastolic flow edge is the flow velocity integral; in response to adenosine, it increased by ≥ 2.5 times

baseline value, a normal response to pharmacotherapy that elicits maximal coronary reserve. Determination of coronary reserve has significant clinical importance in the follow-up of patients with syndrome X who have undergone cardiac transplantation (especially during episodes of rejection),²⁶ patients with left ventricular hypertrophy, and those with atypical chest pain syndromes.²⁶

Assessing angiographically indeterminate coronary lesions: Following coronary angioplasty, the angiographic appearance of the dilated lesions may be hazy or have some intimal disruption, results that are indeterminate. In this setting, coronary flow velocity can be used to determine flow characteristics across the lesion as well as the response of the vessel to pharmacotherapy; this will potentially identify vasospasm and/or impending occlusion due to mechanical obstruction or thrombus.



APV = 20.2

Figure 3 illustrates the angiographic and flow velocity correlations in a patient who underwent angioplasty for a proximal 95% stenosis of the right coronary artery (Figure 3A, top). Corresponding coronary flow velocity before the procedure (Figure 3A, bottom) demonstrated an impaired peak diastolic flow and diastolic-to-systolic flow ratio of 0.9 (normal > 1.5). After the initial balloon dilation (Figure 3B), the angiographic results appeared adequate but the coronary flow velocity, measured within the region of the stenosis, showed a high-velocity jet. Peak flow velocity increased from approximately 20 to 90-100 cm/sec and a residual 30 mm Hg pressure gradient was also measured. After further dilations, angiography showed normal patency. The distal flow velocity had increased, with restoration of the normal diastolic-predominant pattern (Figure 3C).

Further, results of a preliminary study at the J.G. Mudd Cardiac Catheterization Laboratory indicate that proximal-to-distal flow-velocity ratios correlate with lesion gradients (Table I).25

Determining coronary collateral flow and response to pharmacotherapy: Coronary collateral flow was first identified clinically with intracoronary Doppler ultrasonography in 1991.^{22,23} The typical coronary collateral flow-velocity response was characterized by a flow reversal, or persistent antegrade flow, during arterial balloon occlusion; the reversed flow pattern depended on the source of collaterals. Figure 4 illustrates the coronary collateral flow observed after crossing a 95% stenosis of the right coronary artery; the Doppler angioplasty guide wire is positioned beyond the lesion in a posterolateral branch (Figure 4A, open arrow). Coronary flow velocity proximal to the lesion was

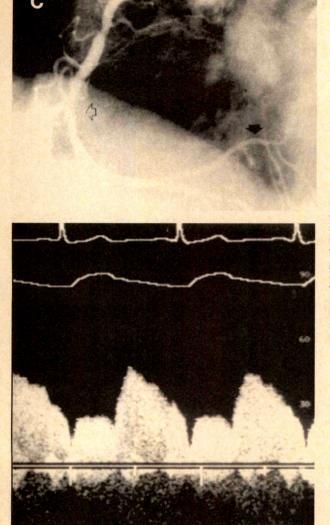


FIGURE 4. A: Anglogram (top) demonstrating 95% stenosis of the mid-right coronary artery (solid arrow) and corresponding flow velocity pattern (bottom). Velocity scale is 0–160 cm/sec. Note the diminished diastolic/systolic flow velocity ratio. Open arrow shows distal position of Doppler guide wire. B: During balloon inflation, Doppler flow velocity is reversed with a maximum velocity of –25 cm/sec; this pattern was reproducible. C: Flow velocity is normalized after completion of successful angioplasty. Note large posterolateral branch (solid arrow) that was input source of collateral flow. APV = average peak velocity. (Reprinted with permission from Am Heart J.²²)

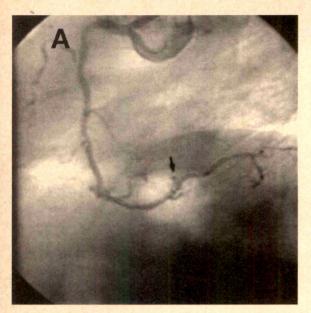
APV = 27.2

impaired (Figure 4A, bottom); peak diastolic and systolic flow velocities were approximately 30–35 cm/sec. During balloon inflation (Figure 4B, bottom), coronary flow-velocity reversal occurred, with a peak negative flow velocity of approximately –25 cm/sec. This flow pattern recurred during multiple balloon occlusions. At the conclusion of the angioplasty procedure (Figure 4C), the coronary stenosis was reduced to <10% and a large, patent distal posterolateral branch was revealed. Restoration of the normal coronary flow-velocity pattern was evident.

Further studies on the use of pharmacotherapy to assess coronary collateral flow during periods of myocardial ischemia are under way. Donohue et al²³ examined the effects of adenosine (and nitroglycerin) administration during balloon occlusion in patients with collateral flow reversal (Table II).

These researchers observed a novel sequence of coronary collateral flow responses. Angiograms (Figure 5) show the left-to-right coronary collateral flow supply feeding the posterior descending artery. The Doppler guide wire, inserted beyond the obstructed branch in the right coronary artery, measured flow during balloon occlusion. The contralateral left coronary artery was cannulated to allow administration of vasodilative drugs. Pressure measurements were also obtained during balloon occlusion and repeat drug administration.

At baseline, the coronary collateral pressure was approximately 45 mm Hg (Figure 6, top left). Baseline coronary flow velocity during balloon occlusion was partly bidirectional, indicating both antegrade (40 cm/sec) and retrograde (-20 cm/sec) coronary flow (Figure 6, bottom left). During injection of 12 µg of adenosine into the contralat-



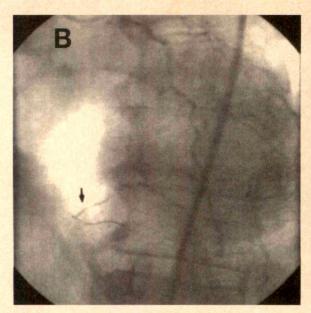


FIGURE 5. Angiograms of right coronary artery with posterior descending coronary artery occlusion at baseline (arrow, left). Contrast injection of the left coronary artery shows collateral filling of distal right coronary artery (arrow, right) where collateral velocity is measured.

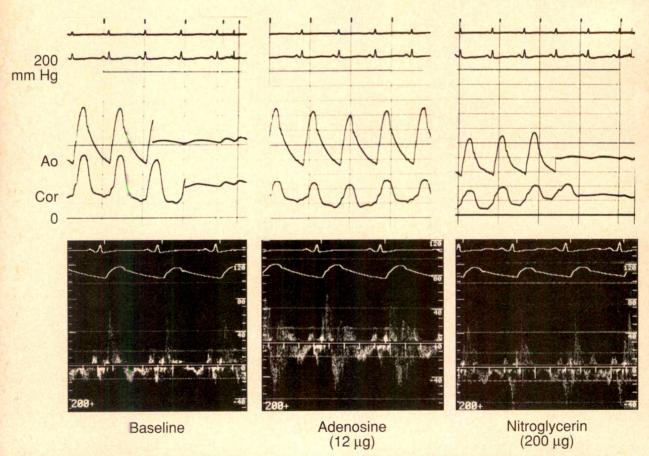


FIGURE 6. At the time of anglography in Figure 5, aortic (Ao) and distal coronary (Cor) pressures were measured at baseline and during left intracoronary adenosine and nitroglycerin administration (scale 0-200 mm Hg). Bidirectional flow velocity patterns occurred during balloon occlusions (bottom). The negative flow (reversal) represents coronary collateral flow. See text for details.

TABLE I Determination of Hemodynamic Significance of Intermediate Stenosis by Intracoronary Doppler Flow Velocity

	Stenosis		Proximal		Distal		
	(%)	Gradient	AV	DV	AV	DV	AV _P /AV _D
Intermediate lesions (n = 17)	(40–60)	12 ± 9	27 ± 10	51 ± 8	24 ± 8	46 ± 12	1.2 ± 0.5
Severe lesions (n = 16)	(>70)	46 ± 20	37 ± 24	62 ± 23	11 ± 7	20 ± 8	3.6 ± 1.3*
p Value		0.001	NS	NS	0.001	0.001	0.001

*Distal velocity reductions and ratios > 2.3 predicted significant hemodynamic gradients.

AV = average velocity; DV = diastolic velocity (centimeters per second); AV_P/AV_D = proximal to distal ratio; NS = not significant. Reprinted with permission from J Am Coll Cardiol.²⁵

TABLE II Perturbations of Coronary Collateral Flow Velocity **During Angioplasty***

	Baseline	Adenosine (2.5 mg)	Balloon Occlusion
Peak velocity (cm/sec)	19 ± 17	17 ± 17	32 ± 26†
Change from baseline (%)	_	-9 ± 14	86 ± 34†

*Six patients with angiographic collaterals with proximal and distal velocities of 25 ± 14 and 4 ± 1 cm/sec (p <0.05) had flow velocity determined during intravenous administration of adenosine and again on serial balloon occlusion. Adenosine had little effect on flow; however, serial balloon occlusions increased collateral flow, demonstrating that hemodynamic effects contributed more than pharmacologic

perturbations on collateral flow velocity.

†p < 0.05 vs baseline; p < 0.05 vs adenosine.

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eral left artery, the distal coronary pressure decreased (Figure 6, center), which caused an increase in coronary gradient and augmented coronary collateral flow velocity to -45 cm/sec (Figure 6, bottom center). Nitroglycerin, 200 µg, introduced into the contralateral artery reduced both systemic perfusion (aortic) pressure and distal coronary occlusion pressure (Figure 6, top right) but did not augment collateral flow velocity as much as did adenosine (-30 vs -45 cm/sec,respectively). Serial balloon occlusions increased collateral flow more than vasodilators. Although these studies are preliminary, the potential for assessing collateral responses to pharmacotherapy with Doppler coronary flow velocity is substantial.

Other unique applications of intracoronary Doppler studies will include assessment of coronary flow velocity in saphenous vein grafts, internal mammary arteries, and during intraaortic balloon pumping.²⁴ Qualitative results of pharmacotherapy administered during any of these conditions will also be available to assess concomitant antiischemic influences of treatment.

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Significance of Silent Myocardial Ischemia After Coronary Artery Bypass Surgery

Donald A. Weiner, MD

The prevalence and prognostic significance of transient myocardial ischemia after coronary artery bypass grafting (CABG) were evaluated. In 3 studies, ischemia was found in an average of 24% of patients by ambulatory electrocardiographic monitoring at 3-12 months after CABG. An average of 36% of patients in 3 other studies experienced ischemic ST-segment depression during exercise testing at 4-50 months after CABG. Of the ischemic episodes, 77% were silent during exercise testing. In the Coronary Artery Surgery Study (CASS) randomized patient subsets, survival at 12 years was significantly lower for patients who had either silent or symptomatic ischemia during exercise testing at 6 months after CABG compared with those who had no ischemia. (Am J Cardiol 1992:70:35F-38F)

yocardial revascularization using coronary artery bypass grafting (CABG) usu-Lally provides excellent symptomatic relief for patients with angina pectoris. Amelioration of myocardial ischemia and improvement in exercise capacity after CABG have been well documented by exercise testing.² Recent studies, however, have determined that transient myocardial ischemia may occur spontaneously or be precipitated by exercise testing in up to 33% of patients postoperatively.3-7 The probable mechanisms involved include graft occlusion, progression of coronary artery disease (CAD) in the native coronary blood vessels, and incomplete revascularization, but unknown factors may also be involved.6

Because postoperative ischemia can be ameliorated or completely abolished by medication, percutaneous coronary angioplasty, or a second CABG, it is important to establish whether postoperative ischemia has an adverse effect on the survival of patients who have undergone CABG. This article will review the prevalence and prognostic significance of postoperative ischemia that has been documented by either exercise testing or ambulatory electrocardiographic (ECG) monitoring.

PREVALENCE

Earlier studies that used ambulatory ECG monitoring after CABG demonstrated that transient myocardial ischemia frequently occurs (Table I). Crea et al,³ using 48-hour ambulatory ECG monitoring in 45 patients an average of 4 months after CABG, found that 68 ischemic episodes occurred in 7 patients (16%). Before CABG, 249 episodes of transient ST-segment depression were observed in 35 patients. Egstrup⁴ applied 36-hour ambulatory ECG monitoring 3 months after CABG in 36 patients who either were asymptomatic or had minimal symptoms and found 39 episodes of silent ischemia among 12 patients (33%). Finally, Kennedy et al⁶ employed ambulatory 24-hour ECG monitoring in 94 patients 3 months (early) after CABG and in 184 patients 12 months (late) after CABG. Silent ischemia was detected in 19 (20%)

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TABLE I Prevalence of Myocardial Ischemia During Ambulatory Electrocardiographic Monitoring After CABG

Study	Patients (n)	Months After CABG	Prevalence
Crea et al ³	45	4	16%
Egstrup ⁴	36	3	33%
Kennedy et al ⁶	94	3	20%
	184	12	27%

TABLE II Prevalence of Myocardial Ischemia During Exercise Testing After CABG

Study	Patients (n)	Months After CABG	Prevalence
Crea et al ³	45	4	36%
Dubach et al ⁵	296	50	28%
Weiner et al ⁷	174	6	36%
	137	18	45%

TABLE III Prognosis for Myocardial Ischemia During Ambulatory Electrocardiographic Monitoring After CABG

Study	Follow-Up	Rate of Cardiac Events
Egstrup⁴	9 months	50% in patients with SMI vs 8% in patients without SMI (p = 0.005)
Kennedy et al ⁶	4 years	Early after CABG: 11% in patients with SMI vs 24% in patients without SMI (p = NS)
		Late after CABG: 14% in patients with SMI vs 15% in patients without SMI (p = NS)

CABG = coronary artery bypass grafting; NS = difference not significant; SMI = silent myocardial ischemia.

TABLE IV Prognosis for Myocardial Ischemia During Exercise Testing After CABG

Reference	Follow-Up (years)	Results
Dubach et al ⁵	2	Prevalence of ST-segment de- pression similar in patients with cardiac events (27%) and in total population (28%)
Weiner et al ⁷	12	Survival worse in patients with symptomatic (45%) or silent (68%) ischemia vs those without ischemia (80%)

of 94 patients early and in 50 (27%) of 184 patients late after CABG. The mean frequency of episodes was in the range of 6-10 per 24-hour period, with a mean duration from 15-23 minutes.

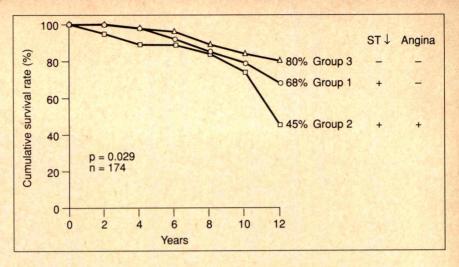
Myocardial ischemia can also be precipitated during exercise testing after CABG (Table II). Crea et al,³ in accordance with a modified Bruce protocol, had 45 patients perform a treadmill test an average of 4 months after CABG; these researchers found ischemic ST-segment depression in 16 (36%) patients. All patients with an ischemic response were incompletely revascularized. Dubach et al⁵ found that 84 (28%) of 296 patients displayed ischemic ST-segment depression when tested according to a standard treadmill protocol an average of 4.2 years after CABG. Fifty (60%) of the 84 patients with ischemia did not have accompanying angina. In a subset of patients in the Coronary Artery Surgery Study (CASS) who were randomized to surgery, treadmill testing according to the Bruce protocol detected ischemic ST-segment depression in 62 (36%) of 174 patients at 6 months (early) after CABG and in 61 (45%) of 137 patients at 18 months (late) after CABG. Silent ischemia during exercise testing occurred in 82% of the ischemic patients studied early and in 90% of the ischemic patients evaluated late after CABG.

PROGNOSIS

Egstrup⁴ found that although 6 (50%) of the 12 patients who showed evidence of silent myocardial ischemia during ambulatory ECG monitoring after CABG experienced cardiac events during the following 9 months, only 2 (8%) of 24 patients without silent myocardial ischemia had such events (Table III). Silent ischemia was the most powerful predictor of cardiac events. In contrast, Kennedy et al⁶ did not find that silent myocardial ischemia predicted adverse clinical events during the first 4-5 years after CABG. The only variable that carried a slightly increased relative risk was younger age in the group tested 1-3 months after CABG.

Two recent studies evaluated the prognostic significance of exercise testing after CABG (Table IV). Dubach et al5 found that the prevalence of ST-segment depression was similar among patients who either died or had a nonfatal myocardial infarction (7 [27%] of 26 patients) compared with the total population (84 [28%] of 296). That study, however, was limited by both the long time (mean 4.2 years) that elapsed between CABG and performance of the exercise test and the short follow-up period (mean 2 years). Data from the CASS randomized population (n = 174) demonstrated that the 12-year survival rate after CABG was significantly different among patients grouped on the basis of the 6-month postoperative exercise test results.⁷ The survival rate was significantly higher for patients without ischemia (80%) than for pa-

FIGURE 1. Cumulative survival rates for patients with silent ischemia (group 1), symptomatic ischemia (group 2), and no ischemia (group 3). n = total number of patients; ST | = ST-segment depression. (Reprinted with permission from J Am Coll Cardiol.7)



tients with symptomatic ischemia (45%) or silent myocardial ischemia (68%) (Figure 1).

DISCUSSION

Results from earlier studies show that exercise testing often produced inaccurate indications of the effectiveness of CABG revascularization. Mc-Conahay et al⁸ found that only 32% of patients with incomplete revascularization and 30% of patients with no revascularization had positive exercise test results. Dodek et al9 found that 33% of patients with complete revascularization had positive exercise tests, and 59% of patients with incomplete revascularization had negative tests. Block et al¹⁰ found that 13 (68%) of 19 patients with unsuccessful revascularization had negative STsegment responses postoperatively.

More recent studies evaluating the prevalence and prognostic significance of ischemia after CABG demonstrate that ischemia occurs frequently after CABG and is usually silent. Although the mechanisms underlying the occurrence of silent myocardial ischemia after CABG are unknown, they may have a neurogenic basis or result from a reduction in the amount of jeopardized myocardium after successful revascularization. In the CASS study, 24 (27%) of the 90 patients who demonstrated symptomatic ischemia preoperatively had silent myocardial ischemia during exercise testing 6 months after CABG.⁷ Therefore, patients who reveal only silent myocardial ischemia postoperatively may be incompletely revascularized, despite the overall lessening of their ischemic burden.

Studies analyzing the prognostic significance of postoperative ischemia have produced conflicting results. In the CASS subset followed up for as many as 12 years after CABG, the occurrence of ischemia during exercise testing predicted an adverse effect on survival.⁷ These results are of particular clinical importance because many treatment approaches, including use of antianginal medications, coronary artery angioplasty, and a second CABG, can successfully lessen or eliminate ischemia. The best strategy for lowering the risk of adverse cardiac events among patients with postoperative ischemia is uncertain at present.

In conclusion, silent ischemia can often be seen during ambulatory ECG monitoring or exercise testing after CABG. Certain investigations have demonstrated that ischemia has an adverse effect on survival, which confirms similar results in studies of patients with stable 11,12 or unstable 13,14 angina and of postinfarction patients. 15,16

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The Council for Myocardial Ischemia and Infarction: Advisory Group Reports on Silent Myocardial Ischemia, Heart Rate Control, and Post–Myocardial Infarction Management

Prakash C. Deedwania, MD, John S. Schroeder, MD, William E. Boden, MD

his yearly report from the advisory groups of the Council for Myocardial Ischemia and Infarction reflects the Council's continued interest in silent ischemia, acute intervention, and postmyocardial infarction management. The Council reviews ongoing research in an effort to translate recent results into current, practical approaches to treatment. Some of its current consensual statements resemble those of the 1991 report. Research on silent myocardial ischemia, for example, continues to question whether treatment can modify its negative prognosis. Stratification of the postmyocardial infarction patient according to the use of thrombolytic therapy and then by type of infarction is still considered a reasonable approach. Certain guidelines, however, have been reinforced by new data and experience. For example, the pharmacologic options available for heart rate control have recently increased, engendering a reexamination of therapy with digoxin, traditionally the optimum treatment for atrial fibrillation.

SILENT ISCHEMIA

Silent myocardial ischemia (SMI) has been recognized as the most common manifestation of coronary artery disease (CAD), having an estimated prevalence of 40–50% among patients with chronic CAD. However, the optimum approach to this type of myocardial ischemia has not been established definitively. Because data are still being gathered in this field, the algorithm endorsed by Advisory Group consensus in 1991 is still current (Figure 1). This algorithm outlines a general

approach that begins by screening for the presence of ischemia and continues, if ischemia is present, by determining whether it carries a high or low risk. Medical therapy and yearly monitoring can be used to manage low-risk ischemia. High-risk ischemia, however, requires measurement of the extent of CAD, which may necessitate revascularization in addition to medical therapy. Research into refining the management of SMI is ongoing. The Advisory Group reviewed the extant knowledge of SMI and emphasized some of the most promising new avenues of investigation.

The significance of SMI lies in its association with a higher risk of coronary events. Several studies have shown that transient episodes of ischemia, whether silent or not, adversely affect clinical outcome in a variety of populations, including patients with stable and unstable angina as well as survivors of myocardial infarction.²⁻⁷ Although the prognostic significance of SMI that occurs following coronary artery bypass grafting has been debated, a new study has shed some light on this controversy. An analysis of a subset of 174 patients from the Coronary Artery Surgery Study (CASS) found that coronary artery bypass grafting diminished the frequency of symptomatic ischemia but not of silent ischemia.8 The overall prevalence of symptomatic ischemia dropped from 52% before surgery to 6% after the procedure, but the prevalence of SMI changed only from 30% to 29%. Moreover, the presence of SMI had a significant adverse impact on subsequent prognosis. At 12 years after surgery, patients without ischemia had a survival rate of 80%, compared with 68% for patients with SMI and 45% for patients with symptomatic ischemia. Whether intervention with drug therapy will ameliorate the adverse prognosis of SMI is not known and thus deserves further investigation.

To target therapy more precisely, other ongoing research is attempting to define the pathophysiol-

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ogy that engenders SMI. In general, ischemia develops as a result of an imbalance between coronary blood flow and myocardial oxygen demand. In direct contrast to the original concept of SMI genesis, an increase in myocardial oxygen demand rather than a decrease in oxygen supply (e.g., from coronary obstructions) is the significant factor in SMI pathophysiology.^{9,10} The role of increased myocardial oxygen demand is evident from the increases in heart rate and systolic blood pressure that often precede the majority of ischemic events during daily life. However, roughly 33% of such ischemic events may not be associated with these hemodynamic increases, suggesting that a decrease in coronary blood supply may yet play an engendering role in ischemia. 11 This dual mechanism may have implications for therapy.

A number of antianginal drugs, particularly β blockers, can reduce or eliminate the frequency and duration of SMI.¹² Of late, attention has focused on calcium antagonists because of their ability to control heart rate and modify coronary vasomotor tone. A recent study involving 60 patients with stable CAD measured the effect of 2 weeks of diltiazem therapy on SMI.¹³ The results showed that diltiazem decreased the total number of silent ischemic episodes by 50% in 70% of patients and reduced the cumulative duration of asymptomatic episodes significantly, from a mean of 78.5 to 24.5 minutes (p = 0.001).

A preliminary analysis of data from an ongoing study being conducted at 30 centers in the United States focused on the prevalence of ischemia (Pepine CJ. Personal communication). In roughly 1,000 patients who had CAD and exercise-induced ischemia, asymptomatic ischemia (defined as 2 epi-

sodes of ≥ 5 minutes) occurred during the daily lives of approximately 1 in 4 of the patients whose condition was clinically stable.

The greatest gap in the current understanding of SMI is whether treatment of ischemia is associated with an improvement in outcome. To address this issue the National Heart, Lung, and Blood Institute has initiated the Asymptomatic Cardiac Ischemia Pilot trial. The primary objective of this multicenter trial is to establish the feasibility of a randomized clinical trial of therapies for asymptomatic myocardial ischemia to reduce mortality and the rate of nonfatal myocardial infarction occurrence. The therapies being studied include anginaguided therapy (current conventional therapy), treatment guided by angina plus evidence of ischemia on ambulatory electrocardiography, and revascularization. The primary endpoint in the pilot study is evaluation of ischemic episodes during 48-hour ambulatory electrocardiographic monitoring at 12-week follow-up. The patient population will consist of men and women < 81 years old who have angiographic evidence of CAD and exerciseinduced ischemia as well as ischemia present on ambulatory electrocardiographic monitoring. The study design (Figure 2) involves treatment with diltiazem and isosorbide dinitrate or atenolol and nifedipine. The Advisory Group has concluded that until results are available, it is reasonable to assume that ischemia is never beneficial and reducing its occurrence may improve patient outcome.

HEART RATE CONTROL

The pharmacologic options for managing atrial fibrillation have been expanded by the intro-

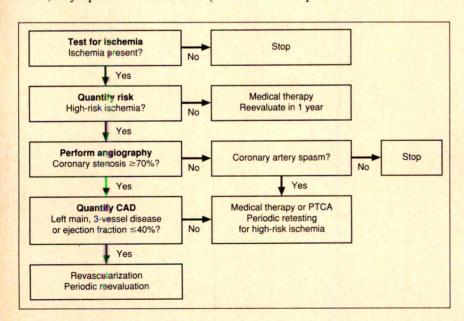


FIGURE 1. Consensual algorithm for management of patients at ischemic risk. CAD = coronary artery disease; PTCA = percutaneous transluminal coronary angloplasty.

duction of intravenous diltiazem to the currently available options of intravenous forms of digoxin, esmolol, and verapamil. Since rapid control of ventricular rate is important, not only to control symptoms but to reduce ischemia, the Advisory Group on Acute Coronary Syndromes has developed an algorithm for management of acute atrial fibrillation (Figure 3).

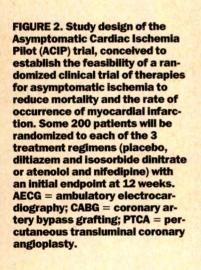
The initial treatment goal is a decrease in heart rate to 80–100 beats/min as quickly as possible. When adequate control is established with acute and, later, long-term use of a drug, pharmacologic or direct current cardioversion may be attempted, if indicated. Therefore, the sooner heart rate control is achieved, the sooner attention can be focused on anticoagulation and long-term treatment. The ideal agent for this purpose should have a rapid onset, be effective in both the emergency department and intensive care unit, result in a sustained reduction in heart rate, and be easy to administer without adverse effects on hemodynamics, cardiac function, or blood pressure.

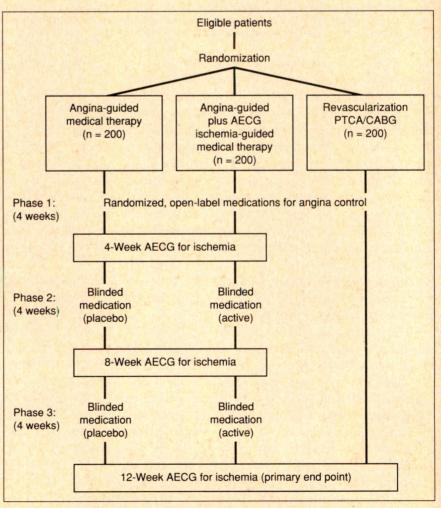
The therapeutic role for digoxin, the original "gold standard" for treatment of atrial fibrillation,

is somewhat diminished today. Although digoxin is inexpensive and its action is predictable, exerting its acute effect by increasing vagal tone, ¹⁴ its delayed onset of action (3–4 hours) is particularly noticeable in settings in which patients have increased sympathetic tone, such as are seen in the emergency department and intensive care unit. Additional drawbacks to digoxin use are a narrow therapeutic window and the possibility of interaction with other agents, such as antiarrhythmic and antihypertensive drugs (e.g., quinidine and verapamil).

Intravenous β blockers, particularly esmolol, offer alternatives to digoxin use. Esmolol has a rapid onset of action and can be administered in a series of increments because of its short half-life. Beta blockers are indicated for atrial flutter or fibrillation and should have a beneficial effect on myocardial ischemia, but side effects (e.g., nausea and hypotension) frequently prevent adequate dosing.

The calcium antagonists that slow atrioventricular conduction significantly increase the options for controlling heart rate. Intravenous verapamil rap-





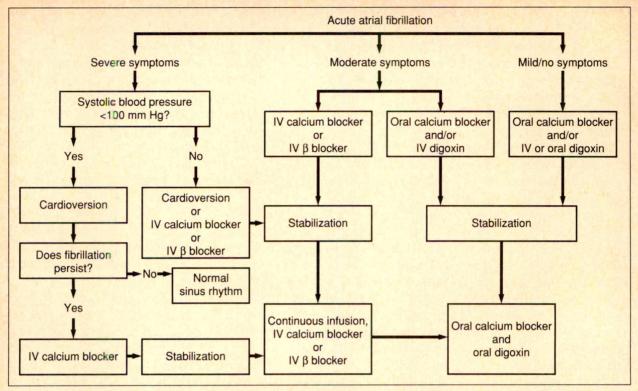


FIGURE 3. Algorithm for the control of heart rate in acute atrial fibrillation. With severe symptoms, cardioversion is necessary. In patients with moderate-to-severe symptoms who do not require cardioversion, choices include intravenous administration of calcium antagonists, β antagonists, or digoxin. Oral calcium antagonists and intravenous or oral digoxin are options for mild symptoms. Calcium antagonists are contraindicated in patients with preexcitation (wide QRS segment) or congestive heart failure.

idly slows heart rate, is safe in patients with chronic obstructive pulmonary disease and diabetes, and has antiischemic and antihypertensive effects. Because of its negative inotropic effects, verapamil must be administered with caution in patients who have abnormal left ventricular function, congestive heart failure, or recent myocardial infarction. Continuous verapamil use concomitantly with digoxin can also lead to digitalis toxicity. Intravenous diltiazem, however, has only a moderate inotropic effect and little effect on serum digoxin levels and thus can be used safely with digoxin. 16,17 Unlike the repeat bolus administration schedule of verapamil, a diltiazem regimen offers the advantage of dosing with an initial bolus that can be followed by continuous infusion of the drug.

The overall approach to the acute management of patients with atrial fibrillation is influenced by the results of the clinical evaluation, the urgency of the situation, and the pharmacology of available agents. Treatment begins with cardioversion of hemodynamically unstable patients, such as those presenting with pulmonary edema or hypotension (Figure 3). In patients with moderate to severe symptoms who do not require cardioversion, use of an intravenous calcium antagonist (diltiazem or verapamil) or an intravenous β blocker is beneficial;

intravenous digoxin is a secondary choice because of its late onset of action. Use of oral calcium antagonists and intravenous or oral digoxin are options for control of mild symptoms. Once atrial fibrillation is controlled, elective cardioversion can be considered.

The options for controlling heart rate today are more flexible and wider in range than ever before. However, the benefits of maintaining sinus rhythm in any patient should always be balanced against the risks of proarrhythmic and other adverse drug effects, and patient tolerance must be considered.

POST-MYOCARDIAL INFARCTION

Secondary prevention remains a major issue in management of the post-myocardial infarction patient. Ongoing research supports the treatment approach this Advisory Group endorsed in 1991 (Figure 4). This approach is in agreement with joint guidelines published by the American College of Cardiology (ACC) and the American Heart Association (AHA).¹⁸ Several key strategies have emerged for the management of postinfarction patients.

The decision for or against thrombolytic therapy occasions the first subset division of postinfarction patients. The optimum treatment for postthrombolytic patients is still a matter of controversy. Although aspirin use is recommended following streptokinase administration, there are supporters of the use of intravenous metoprolol, followed by oral metoprolol, immediately after the administration of tissue plasminogen activator. It is possible that the heart rate-lowering calcium antagonists may emerge as useful adjuncts or alternatives to intravenous β blockers.

In the absence of thrombolysis, it is helpful to dichotomize patients into O-wave and non-Q-wave subsets on the basis of serial electrocardiograms in the cardiac care unit. Further, determining the high-risk versus low-risk status of patients is critical to defining their need for additional invasive or noninvasive testing. Regarding pharmacologic management, the Advisory Group consensus is that the use of B blockers without intrinsic sympathomimetic activity in combination with aspirin is appropriate for secondary prevention following Q-wave infarction.¹⁸ This type of therapy, however, does not reduce mortality or the incidence of nonfatal infarction in patients who have non-Q-wave infarction; the only proven therapy for this group of patients consists of management with diltiazem. 19 Recent subset analysis of the Multicenter Diltiazem Postinfarction Trial (MDPIT) showed that diltiazem lowered cardiac mortality and the incidence of nonfatal infarction in patients who had undergone a first non-Q-wave infarction.20

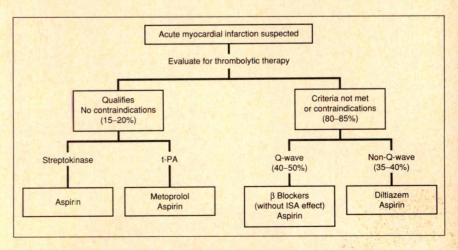
The ACC/AHA recommendations for long-term β blockade are categorized into 3 classes: 1, definite indications; 2, possibly effective indications; and 3, contraindications. Beta blockers are definitely indicated for all patients except those at low risk, for whom the benefit of β blockade is less definite, and those with clear contraindications. Therapy should be initiated within the first few days following infarction and maintained for 2 years. The contraindications for use of β blockers

in the postinfarction setting include: heart rate <60 beats per minute, systolic blood pressure <100 mm Hg, moderate-to-severe left ventricular heart failure, signs of peripheral hypoperfusion, atrioventricular conduction abnormalities (PR interval >0.22 msec, types I and II atrioventricular block or complete heart block), and severe chronic obstructive pulmonary disease. Other relative contraindications include asthma, difficult to control insulin-dependent diabetes, severe peripheral vascular disease, and current use of β blockers or calcium antagonists.

The role of calcium antagonists in treating postinfarction patients is less well defined. The ACC/AHA recommendations list definite indications for symptomatic treatment of postinfarction angina while awaiting cardiac catheterization and therapy based on angiographic findings. 18 Diltiazem, specifically, is recommended as possibly effective in patients with non-Q-wave infarction and no contraindications. Administration should be started within 48 hours of infarction and continued through the first postinfarction year. Calcium antagonist use is also recommended following angioplasty to prevent coronary vasospasm. Use of calcium antagonists may also benefit patients with Q-wave infarction complicated by postinfarction angina who may not be candidates for β-blocker therapy. Infarction complicated by left ventricular dysfunction or pulmonary congestion is a contraindication for therapy with calcium antagonists.

Finally, ongoing studies continue in an attempt to determine the best postthrombolytic therapy. Non-Q-wave myocardial infarction and reperfused myocardium postthrombosis share a number of similarities.²¹ Both conditions are characterized by a high incidence of subtotal coronary occlusion, early creatine kinase washout, preservation of global and regional left ventricular function, histologic evidence of contraction band necrosis, evi-

FIGURE 4. Algorithm for management of the post—myocardial infarction patient. Patients not receiving thrombolytic therapy are divided into 2 subgroups based on electrocardiographic subtype. Patients with Q-wave infarction should receive β blockers without intrinsic sympathomimetic activity (ISA). Those with non-Q-wave infarction should be given diltiazem and aspirin. t-PA = tissue plasminogen activator.



dence of residual ischemia, and inducible ischemia. Future studies may determine that therapy for patients with these conditions is similar.

Despite the need for further clinical trials to define the best postinfarction treatment, the Advisory Group's algorithm (Figure 4) can guide therapy in a reasonable fashion that is in agreement with ACC/AHA recommendations.

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Diagnostic and Therapeutic Implications: Exploration Through Case Discussions

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he following 2 cases of myocardial ischemia were the subject of a discussion under the leadership of William W. Parmley, MD, and Jay M. Sullivan, MD. The following provides the diagnostic and therapeutic highlights of those peer group discussions.

CASE 1 Newly diagnosed cardiac ischemia

HISTORY: G.H. is a 49-year-old white male executive who works for a publisher of medical texts. His cardiac risk-factor profile includes cigarette smoking and a positive family history of cardiovascular disease. He is normotensive, his lipid profile is not known, and he is asymptomatic. His life-style has been sedentary, but during a routine checkup with his family physician, he expressed a desire to start a program of regular aerobic exercise.

PHYSICAL EXAMINATION: Height, 5 feet 10 inches; weight, 195 lb. Pulse regular at 82 beats/min; respirations 14/min; seated blood pressure 132/84 mm Hg. Results of the remainder of the examination were unremarkable.

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LABORATORY ANALYSES: Results of electrocardiography (ECG) were negative. The complete blood cell count and serum electrolyte levels were within normal limits, but the fasting blood glucose level was 140 mg/dL. Given the known cardiovascular risk profile of G.H., his physician recommended obtaining a lipid profile. G.H.'s lipid levels were as follows: total serum cholesterol, 200 mg/dL, highdensity lipoprotein cholesterol (HDL-C), 30 mg/dL, low-density lipoprotein cholesterol (LDL-C), 140 mg/dL, and serum triglycerides, 200 mg/dL.

G.H. was referred to a cardiologist who elected to conduct an exercise stress test. The patient was able to complete only about 7 minutes of exercise and stopped because of fatigue when his heart rate reached 130 beats/min. At the beginning of stage 3 of the Bruce protocol, approximately 2.0 mm of painless ST-segment depression developed, and G.H.'s blood pressure response was normal. Because the patient was asymptomatic, the cardiologist decided to perform 24-hour ambulatory ECG monitoring. Ambulatory monitoring identified 2 episodes of asymptomatic ST-segment depression (≥1.0 mm and >60 sec each) during his usual daily activity.

Discussion of case 1

Dr. Jaffe: The patient has shown evidence of fairly severe ischemia: 2 mm ST-segment depression at a relatively low work load. Cardiac catheterization would provide valuable information regarding the extent of disease.

Risk-factor intervention is probably warranted, and the patient needs to be advised of any changes in his life-style that are required. If lipid-lowering therapy is indicated, consideration should be given to the results of the Helsinki Heart Study, which demonstrated that use of gemfibrozil had a protective lipid-lowering effect in middle-aged men with this type of dyslipidemia.¹

This patient also appears to have borderline diabetes. Patients with insulin-dependent diabetes

Case 1. I otenti	al Management Strategies
Strategy A: Least aggressive	Counsel the patient on the use of nicotine patch (eg, Nicorette) to stop smoking, on weight reduction, and on appropriate diet and other measures to raise his serum levels of high density lipoprotein cholesterol, possibly including use of niacin or gemfibrozil. Since this patient is asymptomatic, however, no intervention other than risk-factor and life-style modification is necessary.
Strategy B: Moderately aggressive	In addition to risk-factor and life-style modification, consider prophylactic use of antiischemic medication, such as a β blocker or calcium antagonist. The potential long-term impact of an antiischemic agent on the patient's lipid profile and probable atherosclero sis may guide selection of an appropriate agent.
Strategy C: Most aggressive	Proceed as in strategy B, but include additional testing, such as radionuclide stress testing and/or coronary angiography, to confirm the presence and extent of coronary artery disease. Results of these tests may also indicate whether revascularization should be recommended.

may have hypertriglyceridemia with chylomicronemia and elevated serum levels of very low density lipoprotein cholesterol. The data suggest that if control of blood sugar levels can be normalized with insulin use, these abnormalities will be at least partly reversed.² Weight reduction may also help (if he is overweight).

Dr. Deedwania: As noted in a recent editorial by William B. Kannel,³ smoking is the most readily modifiable risk factor. Because smoking is a strong predictor of mortality in patients who are at risk for coronary heart disease, it is important to keep that in mind (Table I) for management of this case.

Dr. Higginson: I would recommend performing exercise thallium scintigraphy to determine how much myocardium is at risk and using that information to guide further treatment.

Dr. Boden: I agree with Dr. Higginson's recommendation: one can certainly interpret that this man is in a high-risk group and the results of thallium stress testing would be very helpful. Although his HDL-C level is low, this patient does not meet the National Cholesterol Education Program guidelines for targeted therapy because his total serum cholesterol level falls below the published goal of targeted therapy (≤200 mg/dL).⁴ However, I believe the Helsinki Study strongly indicated that the use of gemfibrozil is associated with improved outcome.¹

Dr. Mehta: High serum triglyceride levels have

been identified as an important cardiovascular risk factor.⁴ Perhaps this patient has the syndrome of diabetes, hypertriglyceridemia, obesity, and hyperinsulinemia—the so-called syndrome X.⁵ He may not have any large vessel coronary artery disease, just typical diabetic small vessel disease that may not be identified on routine coronary angiography.

Dr. Ferlinz: A 12-year study conducted in 740 consecutive patients at Johns Hopkins showed convincingly that "desirable" total serum cholesterol levels of <200 mg/dL are apparently less important than low HDL-C levels.6 In our patient, the cholesterol level is indeed essentially normal at 200 mg/dL, but his HDL-C is quite low at 30 mg/dL, giving us an HDL-C to total cholesterol ratio of almost 1:7 rather than the "ideal" goal of 1:3 suggested by the Framingham Study. About 75% of the patients at Johns Hopkins who had serum HDL-C levels <35 mg/dL had a new adverse cardiac event (either a new myocardial infarction or coronary death), whereas such adverse cardiac events occurred in only 33% of the subjects whose HDL-C levels were higher than normal ($\geq 35 \text{ mg/dL}$). Thus, these results strongly suggest that low serum levels of HDL-C are ominous even when the total serum cholesterol level is within a desirable range; correspondingly, I believe that the inadequate level of HDL-C is the greatest problem in this patient.

CASE 2 'Breakthrough' ischemia

HISTORY: A.G. is a 60-year-old white man employed as a truck driver. He has a 10-year history of hypertension and chronic stable exertional angina; his current treatment consists of metoprolol (50 mg twice daily) and nitrates (isosorbide dinitrate, 20 mg 3 times daily, with sublingual nitroglycerin as needed). A.G.'s hypertension has been well controlled for several years. He experiences an average of 2–3 brief episodes of angina weekly; these episodes occur during periods of strenuous physical exertion or emotional stress and promptly abate with rest or use of sublingual nitroglycerin. This patient smokes.

On treadmill exercise testing 3 years earlier, A.G. attained a maximum heart rate of 120 beats/min and a peak exercise blood pressure of 140/90 mm Hg. He experienced no anginal symptoms and showed no ECG signs of inducible ischemia after 10 minutes of exercise using the Bruce protocol.

Recently, A.G. has noticed an increase in his use of sublingual nitroglycerin. He also reported 2 episodes of angina at rest, each lasting approxi-

mately 5 minutes. He denied any nocturnal anginal symptoms.

PHYSICAL EXAMINATION: Height, 6 feet; weight, 230 lb. Pulse regular at 90 beats/min; respirations, 16/min and mildly labored; and blood pressure, 130/90 mm Hg. The remainder of the physical findings were negative.

LABORATORY ANALYSES: The results of serum lipid determinations, complete blood cell count, and serum electrolyte assays were normal. The patient's resting ECG showed a normal sinus rhythm with baseline ST-segment depression of 0.5–0.7 mm in leads II, III, aV_F, V₅, and V₆. This was unchanged from prior ECG tracings.

Discussion of case 2

Dr. Walsh: Despite his history of a negative treadmill test 3 years previously, I would be very concerned about this man with a 10-year history of angina because of his multiple risk factors. From his history alone, his pretest likelihood of having atherosclerotic disease of the epicardial coronary arteries is >90%. I would be concerned about such a patient, given his history of the quality and quantity of pain at rest.

Dr. Sullivan: There is one confounding issue: the man is hypertensive. There is increasing evidence that hypertensive patients have diminished coronary flow reserve, and that they can experience chest pain in the absence of epicardial coronary disease. Is there anything to suggest that this, and not atherosclerotic progression, might be the cause of his anginal symptoms?

Dr. Boden: His blood pressure is under control at the present time, and the results of his exercise treadmill test 3 years ago show no evidence of a hypertensive blood pressure response.

Dr. Sullivan: Does this presentation warrant the patient's undergoing additional tests as an outpatient, or should he be hospitalized for further evaluation?

Dr. Vokonas: I would take a conservative approach. I would do nothing more than alter his drug regimen and consider obtaining another exercise test (Table II).

Dr. Sullivan: Do these symptoms warrant hospitalization for intensification of medical therapy and/or additional diagnostic testing? Dr Cabin?

Dr. Cabin: I think it depends on the rest angina. If he had 2 episodes of rest angina 2–4 weeks ago and is otherwise fine, I would not say that he required immediate hospitalization. If he called that morning saying that he had experienced his first episode of rest angina the previous night and had experienced a second episode in the morning—

TABLE II Case 2. Pot	ential Management Strategies
Strategy A: Less aggressive	Because the clinical presentation likely represents coronary atherosclerotic disease progression, consider increasing the dosages of the patient's present regimen and/or adding a calcium antagonist. Add aspirin immediately and initiate a smoking cessation program. Reexamine the patient within approximately 2 weeks to determine whether these measures have stabilized his symptoms. After the symptoms have been stabilized, consider repeating an exercise stress test. If the stress test results are again negative, no further action is warranted until a further change in symptoms is observed.
Strategy B: More aggressive	Hospitalize the patient, either in a coro- nary care unit or a telemetry unit. Al- ter drug treatment to include triple antiischemic therapy, use of intrave- nous heparin and aspirin. Perform cardiac catheterization in a timely fashion.

that is a different situation. I might consider increasing the dosages of his medications and performing a cardiac catheterization; before catheterization, I would first ascertain whether his symptoms were controlled. If he does not have high-risk anatomy, I would continue the medical therapy.

Dr. Sullivan: What would convince you that this patient really has rest angina rather than chest pain that is not due to coronary atherosclerosis?

Dr. Cabin: He has had a well-defined pattern of angina for some time. In talking with him, it should be relatively easy to establish whether a change in that pattern had occurred. I think that the acuity of the change is also important.

Dr. Sullivan: When its onset is recent, is exertional angina unstable by definition?

Dr. Cabin: By strict definition, yes. In actuality, no. I think that patients with a recent onset of exertional angina do not require immediate hospitalization.

Dr. Sullivan: I quite agree. Another difficult question involves the necessity for diagnostic studies. Should treadmill exercise testing or rest-exercise thallium scintigraphy be performed, or should the patient have coronary arteriography first?

Dr. Shapiro: If the patient has a recent onset of definite anginal pain at rest that is prolonged, and necrosis is ruled out, I would not hesitate to carry out coronary angiography. If he has unstable angina and has been pain free for ≥ 3 days, then a submaximal, symptom-limited stress test may be performed for risk stratification.

Dr. Walsh: Although patients with unstable angina appear to have a significant incidence of left main coronary artery disease, an equivalent proportion of these patients have normal coronary arteries. Thus, my approach to managing such patients would include coronary arteriography. I would then use the exercise test results prognostically in association with the information revealed by angiography.

Dr. Vokonas: Regarding treatment, I would increase the patient's β-blocker dosage. I often add a calcium antagonist concomitantly and then observe for changes in the patient's condition. Within 1-2 weeks, I would probably consider conducting an exercise test. I would opt for increasing β-blocker therapy first, because this case involves several factors associated with sympathetic nervous system stimulation: smoking, obesity, hypertension, and rapid heart rate. This patient probably has a very stressful job.

Dr. Deedwania: It may be difficult to determine whether this patient previously had episodes of silent ischemia during normal daily activity. For whatever reason, the increased ischemic burden might have made similar episodes more clinically manifest. I think we must recognize that smoking does increase the risk of silent ischemia.7

Dr. Parmley: The most important therapeutic measure for this patient has not yet been mentioned. That is, of course, use of aspirin.

Dr. Cabin: If this patient said that in the past 48 hours he has experienced 2 episodes of angina at rest, I would take an aggressive approach: admit him to the emergency room, administer heparin, and perform cardiac catheterization. On the other hand, if during a routine visit he said that these episodes occurred 2 weeks or 1 month ago, I would simply increase his antianginal medications and initiate concomitant aspirin therapy.

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The American Journal of Cardiology

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Optimizing Antianginal Therapy: A Consensus Conference

GUEST EDITOR:

William H. Frishman, MD

Professor of Medicine and Epidemiology Associate Chairman, Department of Medicine Albert Einstein College of Medicine Montefiore Medical Center Bronx, New York

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Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.

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Optimizing Antianginal Therapy: Consensus Guidelines

The American Journal of Cardiology

Introduction

William H. Frishman, MD

his supplement to The American Journal of Cardiology presents highlights of the conference, "Optimizing Antianginal Therapy," held in Boca Raton, Florida, on February 7 and 8, 1992. Our purpose at this meeting was 2-fold: to present current information on angina pectoris and to try to come to a consensus about its management. Experts presented recent findings from their own research and that of others on a range of angina-related topics, including the pathophysiology of atherosclerosis, the diagnosis of myocardial ischemia, and treatment of angina with nitrates. Workshop groups produced consensus reports on the treatment of unstable and chronic stable angina, the diagnosis of myocardial ischemia, nitrate monotherapy and concomitant treatment, and the recognition and management of nitrate tolerance.

Aram Chobanian discusses new research findings that have shed light on the still-obscure pathophysiology of atherosclerosis. This experimental evidence suggests the importance of oxidized low-density lipoprotein, lipoprotein(a), and several growth factors in the process of plaque formation, and the protective effects of high-density lipoprotein. He points out that although hypertension alone does not appear to promote atherosclerosis, it is a potent promoter of atherogenesis in the setting of hypercholesterolemia.

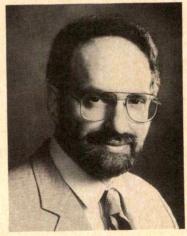
Although transient myocardial ischemia is often experienced as angina, the majority of adverse coronary events occur without this symptom. As Allan Yeung and colleagues explain, these asymptomatic episodes of ST-segment depression are highly associated with the presence of atherosclerotic stenoses of the proximal epicardial arteries in patients with cardiovascular risk factors. They cite

the loss of endothelium-dependent vasodilation as a potential mechanism for transient ischemia and its restoration as an important therapeutic objective in the future management of myocardial ischemia and coronary atherosclerosis.

Traditional wisdom holds that stable angina is associated with a fixed lesion, whereas unstable angina involves mixed mechanisms, i.e., a fixed lesion and vasomotor alterations. Presenting new evidence, Peter Cohn suggests that most angina results from mixed mechanisms, a concept supported by the occurrence of silent ischemia in stable, unstable, and variant angina, despite their differing pathophysiologies.

Carl Pepine reviews current approaches to the measurement of myocardial ischemia, including ambulatory electrocardiographic monitoring, thallium-201 scintigraphy, radionuclide angiography, and echocardiography. Although none of these modalities provides a quantitative measurement of myocardial ischemia, Pepine notes that they can identify functional abnormalities and thus provide a basis for risk stratification.

Appropriate treatment for chronic stable angina depends on accurate risk stratification, as Richard Gorlin notes, explaining that a small



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subgroup of high-risk patients are candidates for surgery, whereas low-risk patients can be managed with medical therapy. The complementary actions of nitrates, \(\beta \) blockers, and calcium antagonists can be harnessed to relieve pain and ischemia, although triple therapy often appears to be no more effective than double therapy. Since endothelial dysfunction probably plays a more important role in chronic stable angina than has been appreciated, Gorlin suggests that nitrates may thus be utilized as adjuvant therapy.

Gary Gerstenblith focuses on the treatment of unstable angina, pointing out that long-acting nitrates, B blockers, calcium antagonists, anticoagulants, and platelet inhibitor therapy have all been shown to be effective. He stresses, however, that the efficacy of therapy must be determined by subjective and objective evaluation in individual patients. Although the advisability of routine revascularization in unstable angina patients awaits the results of the Third Thrombolysis in Myocardial Infarction (TIMI-III) trial, Gerstenblith suggests that those who do not respond to medical therapy or have ongoing disease activity undergo revascularization, noting that it may prolong survival and improve left ventricular function in some patients.

Nitrates have been shown to be of value in patients with ischemic heart disease. Since endothelial function appears to be abnormal in these patients, Jay Cohn proposes that nitrates, which replicate many of the effects of endotheliumderived relaxing factor, be viewed as a pharmacologic replacement for deficient endogenous activity. Nitrates exert a variety of hemodynamic and nonhemodynamic effects that, as Cohn outlines, probably depend on the underlying coronary artery pathology.

Many of these favorable effects of nitrates diminish with continuous use, despite adequate

plasma levels, as I point out in my presentation. This is true, for example, for the transdermal nitroglycerin patch. A recent Food and Drug Administration study provided evidence of tolerance within the first 24 hours of continuous nitroglycerin patch therapy. Tolerance to nitroglycerin and longacting nitrates is marked by an attenuation of both hemodynamic and antianginal effects.

Many factors contribute to the development of tolerance, a phenomenon that appears to be both dose- and time-dependent, according to Uri Elkayam et al. These factors include depletion of sulfhydryl compounds at the vascular cell, nitratemediated increase in blood volume, and neurohormonal stimulation with activation of vasoconstrictive mechanisms.

Ezra Amsterdam describes strategies for preventing nitrate tolerance. The key element, he says, is a nitrate-free interval of 8-12 hours. This technique of intermittent therapy restores vascular responsiveness to nitrates, most likely through recovery of the metabolic mechanisms responsible for their therapeutic effects.

According to pharmacokinetic studies described by Ulrich Abshagen, isosorbide mononitrate undergoes no significant first-pass metabolism and is virtually 100% bioavailable. He describes the drug's pharmacokinetic profile as consistent in different populations and highly predictable in clinical use. The problem of tolerance is circumvented with the use of an asymmetrical, or eccentric, dosage regimen, as discussed by Udho Thadani and Philip de Vane, who review data from recent clinical trials.

It is our hope that these articles and the consensus reports will help clinicians in their efforts to develop a rational and effective approach to the diagnosis and treatment of myocardial ischemia and angina pectoris.

Pathophysiology of Atherosclerosis

Aram V. Chobanian, MD

New experimental evidence has shed light on a number of fundamental processes that contribute to atherosclerotic plaque formation. Recent data suggest that oxidized low-density lipoprotein (LDL) may be more avidly bound and taken up by macrophages, and thus more atherogenic, than unmodified LDL. A subclass of LDL, lipoprotein(a), is also of interest with respect to atherogenic potential, particularly since it has a plasminogen-like moiety as part of its structure. It may promote platelet aggregation and thrombus formation and thereby contribute to atherosclerotic plaque growth. Hypercholesterolemia, hypertension, and possibly other factors may induce changes in endothelial structure and function, which appear to be relatively early events associated with arterial injury. Smooth muscle cell proliferation and accumulation are hallmarks of arterial lesions induced by both hypertension and hypercholesterolemia, and several growth factors have been potentially implicated in these responses. Hypertension by itself causes arterial damage, but it does not appear to induce atherosclerosis when plasma lipid concentrations are low. In combination with hypercholesterolemia, however, it is a potent promoter of atherogenesis, and the mechanisms for this more-than-additive effect are now the focus of considerable investigative attention.

(Am J Cardiol 1992;70:3G-7G)

lthough the etiology of atherosclerosis remains obscure, experimental evidence Apoints to the involvement of several key factors in plaque formation. Circulating lipoproteins play a critical role, and new data suggest especially atherogenic properties for low-density lipoprotein (LDL) that has undergone oxidative modification, as well as for another interesting member of the LDL family, lipoprotein(a), or Lp(a). Yet another important process in the evolution of advanced atherosclerotic lesions involves the release of platelet-derived and other growth factors, with consequent cell proliferation and thickening of the atheroma. Moreover, current knowledge is now closer to elucidating why a combination of risk factors, such as hypertension in the presence of hypercholesterolemia, can be such a potent promoter of atherogenesis. This article explores new evidence about how these diverse mechanisms interact and contribute to the initiation and development of atherosclerosis.

OXIDIZED LOW AND HIGH DENSITY LIPOPROTEIN, LIPOPROTEIN(a), AND **ATHEROGENESIS**

The endothelium appears to play an important role in the events that occur early in atherogenesis. Hypertension, as well as hypercholesterolemia, has been shown to cause changes in endothelial cell morphology and function. Pathophysiologic events leading to endothelial damage include alterations in cell-surface adhesion substances, the so-called endothelial leukocyte adherence molecules (ELAMs), whose expression has been shown to increase in hypercholesterolemic rabbits.1 Permeability changes are also common to most risk factors that cause vascular injury. Such changes may allow LDL to penetrate more readily into the subendothelial space. Early in the atherosclerotic process, chemotactic factors potentially generated by the endothelial cells, smooth muscle cells, and macrophages may attract monocytes and lymphocytes into the subendothelial space. The monocytes can then interact with LDL, particularly of the oxidized type, to become macrophages. Finally, loss of the nonthrombogenic surface is also a

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manifestation of endothelial cell damage that occurs with either hypercholesterolemia or hypertension.

Oxidized LDL: Although macrophages do not exhibit appreciable binding of native LDL, they possess scavenger receptors that bind avidly to oxidized LDL. There is evidence that oxidative modification of LDL occurs within endothelial cells, smooth muscle cells, and macrophages themselves. Several mechanisms have been postulated by which oxidized LDL may contribute to atherosclerosis. High plasma concentrations of LDL lead to increased levels of LDL in the intima. As LDL is oxidized within the arterial wall, it can be taken up by macrophages, which are then transformed to foam cells that accumulate to form fatty streaks.

Oxidized LDL is by itself thought to be cytotoxic and has been implicated in accelerating the formation of fatty lesions. It has also been suggested that, by directly injuring the endothelium, oxidized LDL may facilitate the process by which fatty streak lesions progress to more advanced atherosclerotic lesions. Synthesis of the lipid-infiltration hypothesis and the endothelial-injury hypothesis, as proposed by Steinberg et al,² is presented in Figure 1.

Probucol, an antioxidant agent, has been demonstrated to inhibit the oxidation of LDL. In studies performed in Watanabe heritable hyperlipidemic rabbits, which lack LDL receptors, probucol inhibited the development of these lesions.³ This effect appeared to be independent of the drug's cholesterol-lowering effects, since there was little impact on plasma cholesterol levels in this model. In considering interventions that might retard oxidation of LDL, it is interesting to note that plasma LDL contains its own intrinsic antioxidant compounds, vitamin E and β-carotene. Recent epidemiologic data suggest that intake of high levels of

vitamin E or β -carotene is associated with a lower-than-expected incidence of coronary artery disease, but the findings require confirmation by appropriate clinical trials.

Lipoprotein(a): Lp(a) consists of LDL bound to a unique, highly glycosylated apoprotein, apoprotein A, which has a molecular mass in the range of 300,000–800,000 Da. This plasma lipoprotein fraction has attracted considerable attention, not only because of its epidemiologic status as an independent risk factor for coronary artery disease and cerebrovascular disease, but also because it may represent a pathophysiologic link between atherosclerosis and thrombosis.⁴

The gene for apoprotein A has been localized to chromosome 6, where it appears to be linked to the gene for plasminogen. Especially noteworthy, however, is the structural homology between the lipoprotein and the fibrin-cleaving enzyme. The activation of plasminogen by tissue plasminogen activator is enhanced in the presence of fibrin and also at the endothelial cell surface. Lp(a) has been demonstrated in atherosclerotic lesions. It has been shown to interfere with normal fibrinolysis by binding to fibrin(ogen) and to endothelial binding sites for plasminogen. Thus, it has been hypothesized that Lp(a) not only promotes a chronic prothrombotic state contributing to atherosclerotic plaque growth, but also prevents rapid clot lysis at sites of acute plaque rupture.4

The potential therapeutic advantages of lowering Lp(a) levels remain to be elucidated. Nicotinic acid and neomycin, used singly or in combination, may be effective in lowering Lp(a) levels, although hepatic hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors and anion exchange resins have little impact on this fraction.

High-density lipoprotein: The epidemiologic

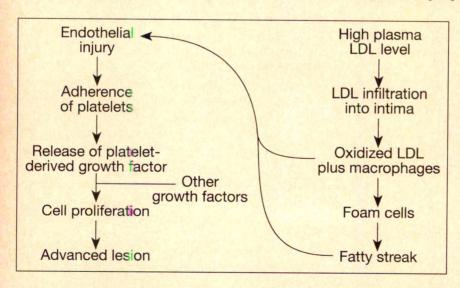


FIGURE 1. The endothelial-injury hypothesis (left) and the lipid-infiltration hypothesis (right) of atherosclerosis: a possible synthesis. LDL = low density lipoprotein. (Adapted with permission from N Engl J Med.²)

data continue to support the inverse correlation between high-density lipoprotein (HDL) levels and clinically significant atherosclerotic disease. A causal relationship has been strongly suggested by recent studies in transgenic mice that express high levels of apoprotein A-I, the major protein component of HDL.5 Transgenic mice fed high-fat diets had elevations in non-HDL cholesterol levels similar to those of nontransgenic control mice of the same atherosclerosis-prone strain who were fed the same diet. However, the increases in plasma apoprotein A-I and HDL levels were more than twice as great in the transgenic as in the control animals. Compared with control mice, the transgenic mice were significantly protected from the development of atherosclerotic fatty streak lesions, suggesting that high apoprotein A-I and HDL levels inhibit the early stages of atherogenesis.

GROWTH FACTORS

Atherosclerotic plaque reflects, at least in part, a complicated pathologic response to vascular injury and healing, involving the interactions of endothelial cells, smooth muscle cells, macrophages, platelets, and lymphocytes. Smooth muscle cell migration, proliferation, and accumulation in the intima occur, along with macrophage accumulation. The stimulation of smooth muscle cell growth may be mediated by growth factors and appears to be a calcium-dependent process. A long list of growth factors, including platelet-derived growth factor, interleukin-1, various cytokines, epidermal growth factor, and transforming growth factor-\u00e3, has been reported to stimulate smooth muscle cell growth. Growth factors may be produced by vascular cells themselves. We have demonstrated increased expression of the platelet-derived growth factor-β receptor and of transforming growth factor-β by northern (RNA) blot analysis in rat aorta in response to blood pressure elevation^{6,7} (Figure 2).

Agents that can inhibit smooth muscle cell proliferation include transforming growth factor-β (which may under certain conditions be a growth promoter), tumor necrosis factor, heparin, angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, colchicine, growth factor antibodies, somatostatin analogues, and high-dose steroids. ACE inhibitors have been shown to inhibit the development of proliferative fibromuscular plaque and preserve lumen integrity after balloon injury to the rat carotid artery.8 Untreated animals who sustained vascular injury showed evidence of smooth muscle cell proliferation, smooth muscle

cell migration from the media to the intima, and extracellular matrix synthesis leading to intimal thickening and reduction in lumen area. The investigators assumed that the effect of the drugs in preventing this restenosis-type lesion was related to inhibition of angiotensin II-modulated smooth muscle cell proliferation and matrix protein synthesis. The calcium antagonist isradipine has been shown to have similar effects on plaque size in rat carotid arteries.9 A more recent report indicated that a polyclonal antibody to platelet-derived growth factor inhibited the development of intimal lesions in rat carotid arteries after balloon injury. 10 These findings confirmed the involvement of endogenous platelet-derived growth factor in the accumulation of smooth muscle cells associated with angioplastic vascular injury.

Beneficial effects have been observed in experimental models of atherosclerosis as well. Our studies have demonstrated that captopril markedly reduced aortic surface involvement by atherosclerosis in the descending thoracic aorta (Table I).11 Treatment also reduced the cellularity and increased the connective tissue content of the atherosclerotic lesions. Similar results have been observed by us with another ACE inhibitor, trandolapril, 12 suggesting a class effect of these drugs.

RISK-FACTOR MODIFICATION AND INTERACTIONS

Studies performed more than 2 decades ago proved that reducing plasma cholesterol levels in hypercholesterolemic animals would markedly reduce arterial cholesterol content. In one such study, monkeys who had been fed a high-cholesterol diet for 40 months developed plasma cholesterol levels of 500-700 mg/dL and severe coronary artery disease. However, in monkeys who were switched to a normal diet after 17 months, plasma cholesterol levels returned to normal, and the coronary arteries showed fewer foam cells, a considerable reduction in cholesterol, some improvement in lumen diameter, and a relative increase in connective tissue content.13

Hypertension induces arterial changes markedly similar to those observed with hypercholesterolemia, including endothelial changes, leukocyte adherence and penetration, macrophage accumulation, increased permeability to plasma lipids, smooth muscle cell migration, and intimal smooth muscle cell proliferation and accumulation. In the presence of normal circulating lipoprotein levels, these hypertensive changes usually culminate in intimal thickening rather than atherosclerotic

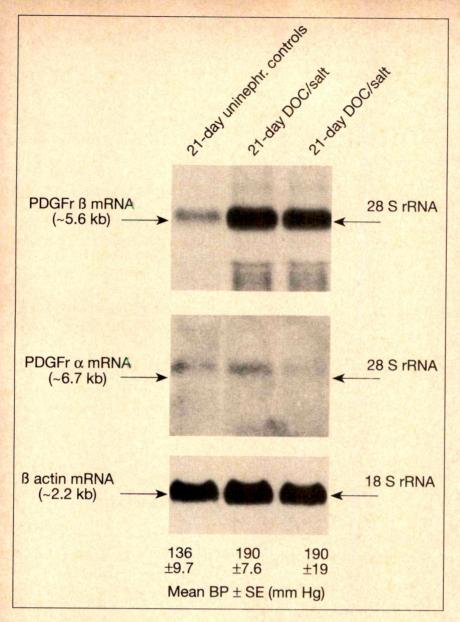


FIGURE 2. Northern blot analyses of aortic platelet-derived growth factor (PDGF) receptor gene expression in deoxycorticosterone (DOC)/salt hypertension; aortic PDGF-r β , PDGF-r α , and β -actin steady state mRNA levels in DOC/ salt hypertensive rats and normotensive uninephrectomized (Uninephr) controls. The mean systolic blood pressure ± SE is shown at the bottom of each lane. Adapted with permission from Hypertension.

plaque development. In association with hypercholesterolemia, however, hypertension can be an important promoter of atherosclerosis. The potency of this combination of risk factors has been demonstrated dramatically in Watanabe rabbits.

TABLE I Effects of Angiotensin Converting Enzyme Inhibitors on Aortic Atherosclerosis in the WHHL Rabbit*

Aortic Region	Control (% intimal surface)	Captopril (% intimal surface)
Total aorta	47.9 ± 3.6	29.7 ± 3.9†
Ascending and arch	76.3 ± 4.7	76.3 ± 3.7
Descending thoracic	48.9 ± 5.2	15.3 ± 3.9‡
Abdominal	28.6 ± 2.5	26.2 ± 4.4

*Eight control and 14 captopril-treated Watanabe heritable hyperlipidemic (WHHL) rabbits

tp < 0.01.

Adapted with permission from Hypertension. 11

The extent and severity of atherosclerotic plaque formation was significantly greater in hypercholesterolemic rabbits who were also hypertensive than in animals who were equally hypercholesterolemic but normotensive.14 In clinical terms, this morethan-additive effect represents an enormous problem, since 40% of patients with untreated hypertension have serum cholesterol levels ≥ 240 mg/dL, whereas 46% of patients with serum cholesterol levels $\geq 240 \text{ mg/dL}$ have blood pressures $\geq 140/90$ mm Hg.15

CONCLUSION

We are now beginning to unravel the exact mechanisms by which hypertension and hypercholesterolemia damage the arterial wall and contribute to the development of atherosclerosis. Recent research has provided exciting insights into the increased atherogenic potential of oxidized LDL, the possible atherogenic and thrombogenic contributions of Lp(a), the protective effects of HDL (even in the presence of elevated total cholesterol levels), and the role of growth factors in inducing smooth muscle cell proliferation and plaque formation and progression. Our enhanced perspective on the interactions among these fundamental processes should eventually lead to improved strategies for preventing or modifying the course of atherosclerosis.

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DISCUSSION

Participant: In your study in Watanabe rabbits, what accounted for the differences in the extent to which angiotensin-converting enzyme (ACE) inhibition affected atherosclerosis in the abdominal aorta and ascending aorta versus the descending thoracic aorta?

significantly decreased atherosclerosis in the descending thoracic aorta but not in the abdominal aorta or the ascending aorta. This may reflect an experimental design problem, in that by the time the animals began treatment at 3 months of age, they had already developed considerable atherosclerosis in the ascending aorta. The opposite situation could hold for the abdominal artery, where it is a slow process that may take longer. However, in our more recent studies with another ACE inhibitor, trandolapril, we have observed statistically significant changes in all 3 arteries, although the greatest changes were still noted in the descending thoracic aorta.

Participant: In the carotid endothelial injury model, a variety of agents have been shown to prevent vascular smooth muscle hyperplasia. However, none of these agents has been shown to be really effective in preventing restenosis after angioplasty in humans. Have you any ideas on why this is the case?

Dr. Chobanian: The recent European study with another ACE inhibitor, cilazapril, certainly did not show any effect of the drug in preventing restenosis, and the results to date with calcium antagonists have been similarly negative. It is unclear whether these negative results stem from problems in study design or drug dosing, or whether they reflect species differences.

New Insights into the Management of Myocardial Ischemia

Alan C. Yeung, MD, Khether E. Raby, MD, Peter Ganz, MD, and Andrew P. Selwyn, MD

Episodes of ST depression are closely related to transient decreases in regional myocardial perfusion during physical or mental stress. At the onset of these events, there is transient constriction of atherosclerotic stenoses, with an increase in myocardial demand as reflected by increases in heart rate and blood pressure. Recent research has shown that normal epicardial coronary arteries respond to these provocations and to increasing blood flow with progressive vasodilation. In contrast, atherosclerotic vessels lose this ability to dilate and may show paradoxical constriction. This abnormal constriction parallels the response of the arteries to acetylcholine, which can be used to assess the ability of the coronary endothelium to regulate vasodilation. The loss of endothelium-dependent vasodilation appears to be an important functional manifestation of coronary atherosclerosis and a potential triggering mechanism for transient ischemia. Dysfunctional endothelium may also result in a procoagulant surface, with cell adherence and local thrombus formation. Restoration of normal endothelial function is likely to emerge as an important therapeutic objective in the management of myocardial ischemia and coronary atherosclerosis.

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ransient myocardial ischemia is an important functional expression of coronary artery disease. Although angina is a typical herald of ischemia, it does not occur prior to the majority of adverse coronary events. Episodes of ST depression are closely related to transient decreases in regional myocardial perfusion in response to such provocations as exercise, exposure to cold, and mental stress. Recent research indicates that atherosclerotic arteries lose their ability to dilate in response to such stimuli and instead constrict inappropriately. Experimental and clinical studies suggest that the loss of endotheliumdependent vasodilation is an important consequence of hypercholesterolemia and coronary atherosclerosis and represents a potential pathogenic mechanism for transient myocardial ischemia. These findings may prove of value in the treatment of myocardial ischemia, the control of atherosclerosis, and the prevention of adverse coronary events.

TRANSIENT ISCHEMIA: PREVALENCE AND **PROGNOSIS**

Most clinicians would agree that, in patients with coronary artery disease, the presence and severity of transient ischemia provide a measure of the risk of adverse coronary events. A familiar clinical problem is that, although the majority of ischemic episodes that occur in middle-aged individuals with cardiovascular risk factors are completely asymptomatic, these transient events are also highly associated with the presence of atherosclerotic stenoses in the proximal epicardial arteries.

The prevalence of ischemia varies greatly, depending on the clinical diagnosis. It is important to emphasize that this prevalence is <10% in unselected populations with no symptoms, no history of coronary artery disease, and few risk factors. For this reason, screening is not worthwhile in these open populations. In contrast, active ischemia during exercise testing or ambulatory monitoring is quite frequent in populations with chronic stable

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coronary disease or unstable angina and among survivors of myocardial infarction, coronary artery bypass grafting, or cardiac arrest. Even in patients who present with peripheral vascular disease, ambulatory monitoring and dipyridamole thallium studies reveal a 16–20% prevalence of unsuspected but active ischemia. Thus, in these high-risk populations, the prevalence of ischemic episodes must be considered, whether or not an individual complains of angina.

In patients with chronic stable coronary artery disease, the severity and extent of ischemia on thallium stress testing correlate with the event rate on subsequent follow-up.4 It is interesting to note that the risk of myocardial infarction or death is extremely low for approximately 2 years in patients with chronic stable coronary disease who have positive exercise tests and proven atherosclerosis but who show no active ischemia on ambulatory monitoring while off medication.5 After 2 years, however, these patients begin to experience adverse events, presumably because of progression of the underlying coronary disease. In contrast, the occurrence of active ischemia on Holter monitoring is associated with a worse prognosis, even when it is the single distinguishing clinical feature. Patients with asymptomatic ischemia show better event-free survival than those with symptomatic ischemia at the outset, but this advantage is lost within 3 years (Figure 1). By 5 years, patients with asymptomatic and symptomatic ischemia experience the same prognosis.

ATHEROSCLEROSIS, ENDOTHELIAL DYSFUNCTION, AND VASOCONSTRICTION

Sympathetic stimulation: What is the role of increased myocardial oxygen demand and decreased coronary blood supply in causing the ischemia associated with such common events as exercise, mental stress, and exposure to cold? These events are almost always accompanied by an increase in neural and circulating sympathetic activity, blood pressure, and heart rate, resulting in increased myocardial demand. At the same time, normal epicardial coronary arteries respond to this increase in demand associated with sympathetic stress with increased coronary blood flow and modest vasodilation of the large epicardial vessels. Atherosclerotic vessels, in contrast, lose this vasodilator response and develop constriction of varying degrees during sympathetic arousal. Interestingly, however, these vessels retain their ability to dilate in response to nitroglycerin.

Evidence from basic as well as clinical research

suggests that endothelial dysfunction in atherosclerosis permits the growth of stenotic lesions and the appearance of paradoxical constriction. The coronary vascular endothelium is a responsive organ that, in and of itself, can transduce signals from the intravascular environment, including blood pressure, pulse pressure, and acetylcholine stimulation of muscarinic receptors. In addition, many products of platelets and thrombin can stimulate the endothelium to exert its own local vasodilating effect on vascular smooth muscle cells. Thus, in the healthy intact organism, the endothelium regulates a defensive local vasodilating response. Within the endothelial cell, in response to appropriate stimuli, nitric oxide is cleaved off the terminal guanidino group of the amino acid L-arginine. The short-lived nitric oxide then diffuses locally, reaching the vascular smooth muscle cells, where it acts on cyclic adenosine monophosphate, producing vasodilation through a mechanism not dissimilar to the therapeutic effects of nitroglycerin. We know from experimental studies that this very fragile and easily disturbed vasodilator system can be impaired by increased levels of low-density lipoprotein (LDL), particularly oxidized LDL; by hypertension; and by the early changes of atherosclerosis.

These findings are directly relevant to coronary artery disease in our patients. Smooth coronary arteries can exhibit endothelium-dependent vasodilation in response to acetylcholine (10^{-8} – 10^{-6} M), a local and specific test of endothelial function, or in response to more complex sympathetic stimuli such as mental stress (Figure 2A). Our group has demonstrated in patients undergoing diagnostic catheterization that atherosclerotic coronary arteries lose their dilator response and develop constriction in response to either acetylcholine or mental stress (Figure 2B). Interestingly, the vasomotor response to mental stress correlates with the

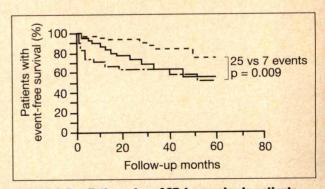


FIGURE 1. Predictive value of ST depression in patients with chronic stable angina. --- = no ST depression; --- = ST depression, asymptomatic; --.-- = ST depression, symptomatic. n=138. (Adapted with permission from Circulation.⁵)

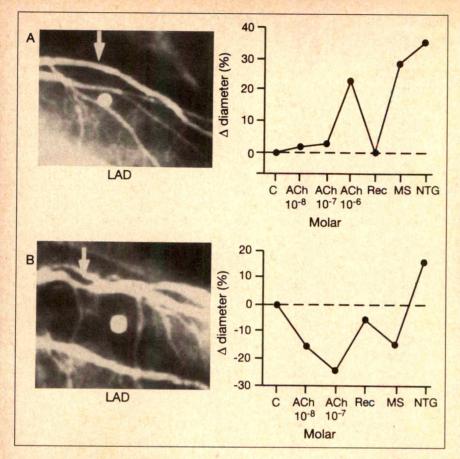


FIGURE 2.A. Response of a smooth left anterior descending (LAD) artery segment to acetylcholine (ACh) and mental stress (MS). B. Response of a stenotic left anterior descending (LAD) artery segment to acetylcholine and mental stress. C = control; Rec = recovery; NTG = nitroglycerin. (Adapted with permission from N Engl J Med.6)

response to acetylcholine (r = 0.58, p < 0.003; Figure 3). Similarly, previous studies have shown that atherosclerosis-induced disturbances in coronary vasomotor function cause abnormal constriction in response to exercise⁷ and to cold pressor testing⁸ and that these responses also correlate with the response to acetylcholine. These observations suggest that the coronary vascular endothelium is an important local determinant in the balance of forces that determine the net response

of the epicardial arteries to physical and mental stressors. Thus, the disruption of local endothelial function by atherosclerosis can impair coronary vasodilation, leading to inappropriate vasoconstriction at stenoses and, possibly, transient myocardial ischemia.

Those arteries with intact endothelial function appear to be resistant to the constrictor effect of phenylephrine administered locally as a sympathetic stimulus. It has been shown angiographi-

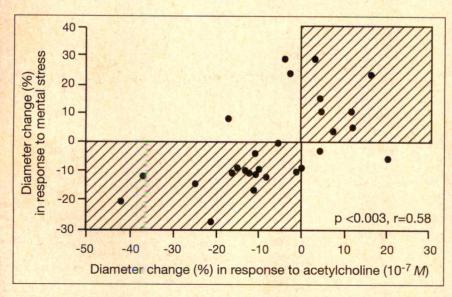


FIGURE 3. Relation between changes in diameter (%) in response to acetylcholine and to mental stress. (Adapted with permission from N Engl J Med.6)

cally, however, that coronary arteries with dysfunctional endothelium are significantly more sensitive to the constrictor effects of identical doses of phenylephrine. These clinical findings, which confirm the results of early animal experiments, may provide one explanation of why paradoxical constriction occurs in coronary arteries with dysfunctional endothelium when challenged by a sympathetic stimulus.

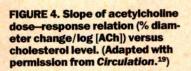
Thrombosis: In the presence of dysfunctional endothelium, paradoxical coronary vasoconstriction results not only from sympathetic stimulation, but also from thrombin produced in the coagulation cascade and from serotonin and adenosine diphosphate elaborated by aggregating platelets. This represents a potentially important link that connects atherosclerosis, thrombosis, and abnormal constriction, these being the important elements leading to ischemia and infarction in our patients with no angiographic evidence of coronary atherosclerosis.

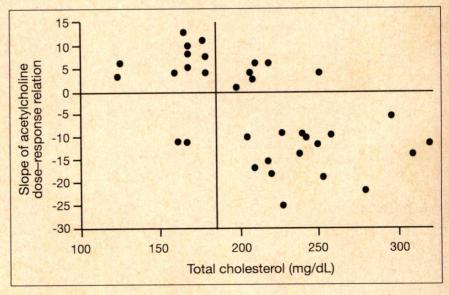
Hyperlipidemia: Endothelial function can be affected by many factors, but most notably plasma lipid levels. In patients with no angiographic evidence of coronary atherosclerosis, total cholesterol <180 mg/dL is generally associated with intact endothelial function, as reflected by a vasodilator response to acetylcholine (Figure 4). On the other hand, in most patients with cholesterol levels > 220 mg/dL, endothelial function is lost even in coronary arteries without angiographic evidence of atherosclerotic lesions. There is both clinical and experimental evidence that endothelial dysfunction occurs very early in the development of atherosclerosis.11 In the macaque monkey, endothelium-dependent vasodilation is lost with hypercholesterolemia but can be restored if hypercholesterolemia is corrected, even in the presence of subintimal thickening, which takes a longer time to regress. ¹² Clinical research studies in patients are currently investigating whether endothelial abnormalities can be reversed and appropriate vasodilator and anticoagulant functions restored in patients with atherosclerosis by administering antioxidants such as probucol, by decreasing LDL levels, and in the future by increasing high-density lipoprotein levels.

Studies in patients show that lowering plasma cholesterol, particularly LDL cholesterol, results in very modest physical regression of coronary atherosclerosis but much more substantial reductions in adverse coronary events.¹³ This suggests that improvements in the functional aspects of the physiology of atherosclerosis are not only possible but are likely more important in patients. The Multiple Risk Factor Intervention Trial (MRFIT), for example, demonstrated that patients with manifest coronary artery disease will benefit from cholesterol lowering, blood pressure control, and smoking cessation.¹⁴ Further support for this concept comes from the more recent Familial Atherosclerosis Treatment Study (FATS),15 which showed that intensive lipid-lowering therapy reduces the frequency of progression of coronary lesions and the incidence of cardiovascular events in men with coronary artery disease who are at high risk.

EFFECTS OF ANTI-ISCHEMIC THERAPY ON PROGNOSIS

Much more is known about the effects of antianginal drugs on ischemia than about their influence on patient outcome. For example, it is known that any decrease in the frequency of ischemic episodes achieved by a β blocker or a dihydropyri-





dine calcium antagonist, or a combination of the 2, is significant and dose-dependent and that various antianginal agents have differential effects on ischemia occurring at low heart rates versus high heart rates. Studies in patients using ambulatory electrocardiographic monitoring have demonstrated that β blockers may actually increase the incidence of ischemic events at low heart rates but exert a beneficial effect on ischemia at intermediate and high heart rates. 16 In contrast, transcutaneous nitroglycerin reduces ischemia at low heart rates but worsens the events at high heart rates. These opposite but complementary actions may stem not only from the drugs' overall effects on heart rate and myocardial demands, but also from differences in their effects on coronary blood supply.

A multicenter study funded by the National Heart, Lung, and Blood Institute is underway and addresses the issue of whether the relief of ischemia can reduce adverse coronary events in patients. At present, there is only minimal evidence that medical therapy affects prognosis, with the exception of \(\beta \) blockers and aspirin in certain subsets of coronary patients.¹⁷ Surgical treatment has been shown to improve survival relative to medical treatment in patients with obvious evidence of ischemia in noninvasive test results, although it offered no advantage in those who had normal or only mildly abnormal test results, i.e., no ischemia.18

CONCLUSION

The dysfunctional endothelium that characterizes coronary atheroslerosis results in the loss of normal endothelium-mediated vasodilator responses to physical and mental provocations and also leads to the development of a procoagulant surface, with cell adherence and local thrombus formation. Active ischemia in patients with coronary lesions appears to arise from this disordered cell biology, i.e., abnormal growth of stenosis, constriction, and thrombosis, all of which increase the patient's risk of adverse outcomes. In the future, the restoration of normal endothelial functions is likely to become a major goal in the long-term control of coronary atherosclerosis and prevention of adverse coronary events.

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DISCUSSION

Participant: Does hypertriglyceridemia, in the absence of hypercholesterolemia, alter the endothelial response to acetylcholine?

Dr. Andrew Selwyn: That is an interesting point, since in some clinical settings hypertriglyceridemia is an independent risk factor for atherosclerosis and for coronary events. There is very little information about the influence of triglycerides on endothelial function, since the majority of studies to date have examined the effects of increased LDL, oxidized LDL, and, to a lesser extent, shear force and blood pressure.

Participant: Have you attempted to block the action of nitric oxide to confirm that it is actually an endothelial function that mediates the vascular response to stress?

Dr. Selwyn: Administration of very small quantities of free hemoglobin and monomethylarginine into the coronary circulation abolishes the vasodilator response to stress, increased blood flow, and acetylcholine. Most studies have shown that the change from dilation to constriction depends on the function or dysfunction of the endothelium. This is not to say that endothelial dysfunction is the only abnormality in atherosclerosis, but it does appear to be a reasonable barometer of atherosclerotic damage.

Participant: Do atherosclerotic coronary arteries constrict in response to stress because they are more sensitive to circulating catecholamines?

Dr. Selwyn: According to the work of Martin et al, 10 in the healthy endothelium, there is continuous basal release of endothelium-derived relaxing factor (ERDF) under normal conditions and pulsed release in response to stress. Loss of the ability of the endothelium to release EDRF accounts for the shift in the vascular dose-response curve to norepinephrine and to phenylephrine.

Participant: Could you summarize your perspective on the heart rate changes that precede episodes of ischemia?

Dr. Selwyn: Most ambulatory monitoring studies have shown that a small increase in heart rate (a median of 15 beats/min) precedes the onset of >70% of episodes of ST-segment depression. These periods of increased heart rate last an average of 30 minutes. In contrast, equal increases in heart rate that are short lived are not associated with ischemia. Thus, unlike ischemic episodes observed during the Bruce protocol, the majority of ischemic episodes that occur outside the hospital appear to be associated with modest increases in heart rate of long duration.

Participant: You described differences in therapeutic response based on the resting heart rate. Are there any differences in heart rate changes in individuals with low versus intermediate versus high heart rates?

Dr. Selwyn: It is difficult to distinguish between the effect of the B blocker because they reduce heart rate throughout the day but could also modify the mechanisms at the onset of ischemia. Beta blockers can reduce heart rate below the range that precedes ischemia. Despite this, ischemia continues to occur at lower heart rates. The puzzle is that the incidence of ischemic events at low heart rates actually increases with β blockade.

Participant: Could you speculate about the adverse effects of the B blockers in increasing atherogenesis at the same time that they protect against rapid heart rates?

Dr. Selwyn: The effect of the β blockers actually represents the net effect of several different actions, including antiarrhythmic activity, anti-ischemic activity, and decreased myocardial oxygen consumption (MVO₂). Theoretically, there is reason to believe that β blockade removes the dilating effect of β stimulation on the epicardial arteries, leaving α constriction unopposed. In fact, coronary resistance is slightly worse at rest during β blocker therapy. However, these effects are balanced by the stronger effect of decreased MVO2 throughout the day. Thus, the net effect is a significant reduction in the overall frequency and duration of ischemia, despite the increased frequency of low heart rate ischemic episodes.

Participant: Could you comment on the clinical implications of the increased frequency of low heart rate ischemic episodes?

Dr. Selwyn: One possibility is that β blockade eliminates high heart rate ischemic events, so that the ischemia that remains simply appears in the lower heart rate range. A second possibility is that B blockers are more effective in abolishing ischemic events triggered largely but not exclusively by an increase in MVO2. Thus, the remaining ischemic episodes are caused primarily by problems with coronary blood supply. It might be of interest to investigate whether such supply-side ischemic events provide important prognostic information and whether they reveal anything about the pathophysiologic activity of the coronary disease at the time they occur.

Mechanisms of Myocardial Ischemia

Peter F. Cohn. MD

Traditionally, myocardial ischemia has been viewed as an imbalance in the supply and demand of myocardial oxygen. Stable angina is usually considered to involve a fixed lesion, whereas unstable angina involves a fixed lesion as well as such components as platelet aggregation, thrombotic processes, and vasospasm. Variant angina involves primarily vasospasm. A newer concept holds that most angina results from mixed mechanisms in which both fixed lesions and vasomotor alterations play a role. These mechanisms are responsible for mixed ischemic events, characterized by episodes at varying levels of exertion, with or without anginal pain. This concept would seem to be supported by the occurrence of silent ischemia in the setting of stable, unstable, or variant angina, despite differing pathophysiologic conditions. Ischemic events have important prognostic significance; unfortunately, many are unrecognized by patients. The question whether the treatment of ischemic events will improve prognosis remains a matter of debate.

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raditional views regarding the mechanisms of myocardial ischemia are being supplanted by a newer concept based on the presence of both fixed atherosclerotic obstructions and vasomotor changes. These factors are thought to be responsible for what has now been termed mixed ischemia—the occurrence of ischemic episodes at varying levels of exertion. Ischemic events are of particular importance because they have adverse prognostic implications but often go unrecognized by patients.

TRADITIONAL CONCEPTS OF ISCHEMIA

The pathophysiologic pattern of myocardial ischemia has traditionally been viewed in terms of an imbalance between myocardial oxygen supply and demand. Any factor that results in greater myocardial oxygen demand or reduced oxygen supply can thereby provoke ischemia.

On the demand side, ischemia may result from an increase in heart rate, contractility, or left ventricular wall stress. The increased demand can be caused by exercise, emotional stress, hypertension, tachycardia, a left ventricular outflow obstruction, or a hypermetabolic state. Myocardial oxygen supply is determined by coronary blood flow and coronary arteriovenous oxygen difference, which is normally near maximal at rest. This supply may be decreased by atherosclerotic coronary obstruction, vasospasm, platelet aggregation, hypotension, anemia, or hypoxia.

CONSEQUENCES OF ISCHEMIA

Pathophysiologic studies have given rise to intriguing findings regarding the biochemical, hemodynamic, electrocardiographic (ECG), and clinical sequelae of myocardial ischemia. Despite the broad range of consequences of ischemia, the prognostic significance of these changes has been a matter of considerable controversy. This debate has centered on the issue of whether ischemia should be treated not simply to relieve anginal pain when that is present, but to reduce the possible risk of morbidity and mortality associated with the ischemia per se.

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With ischemia, the shift from aerobic to anaerobic energy usage results in lactate production and potassium release. The effects of these changes on subsequent clinical events must be considered. In addition, ischemia exerts hemodynamic effects that are not only systolic, but diastolic in nature. These changes include an increase in left ventricular end-diastolic pressure, a decrease in cardiac output, greater diastolic stiffness, and wall-motion abnormalities. Some observers have conjectured that such effects, continuously repeated, might lead to chronic, patchy fibrosis of the ventricle and, ultimately, cardiomyopathy.

The ECG effects not only encompass the STsegment and T-wave changes typical of subendocardial or transmural ischemia, but also can lead to arrhythmias. Although the literature on the progression from ischemia to fatal arrhythmias is, at present, relatively anecdotal, it only requires a single episode of ventricular fibrillation to cause death. Obviously, then, if only 1 episode of ventricular fibrillation occurs over the course of hundreds of episodes of ischemia, this is nonetheless an important prognostic consideration.

The clinical consequences of myocardial ischemia fall into 2 categories: symptomatic (angina) and asymptomatic (silent) ischemia. Again, the question whether therapy is indicated for more than symptomatic relief remains unresolved.

SYMPTOMATIC VERSUS ASYMPTOMATIC **ISCHEMIA**

The sequence of events that occur during myocardial ischemia has been well demonstrated in the angioplasty experience. After occlusion, relaxation and contraction abnormalities occur first, followed by increased filling pressure, ECG changes, and finally angina.1 Although pain is common, patients often do not complain of symptoms during the angioplasty procedure, even when complete occlusion is present.

The reasons for the lack of pain during some ischemic episodes remain unclear. In one study, the anginal perceptual threshold (defined as the time from onset of exercise-induced ST-segment depression to onset of symptoms) was found to be prolonged in diabetic, compared with nondiabetic, subjects.2 The investigators suggested that this altered pain perception might result from damage to the sensory innervation of the heart—a previously unrecognized component of diabetic neuropathy. Notably, however, the perception of anginal pain is highly variable among both diabetic and nondiabetic subjects. Pain perception thresholds

that are sufficiently altered to prevent patients from experiencing angina are likely to be present in only a small group of individuals who rarely have ischemia.

Much more common are patients who experience pain during some episodes of ischemia but not others. Although silent ischemia is more prevalent in diabetic patients and also increases with aging, perhaps due to neuropathy, these observations do not help explain why an individual patient may experience a painful ischemic episode during the day and an asymptomatic episode only 1 hour later.

A series of studies have examined the importance of the amount of myocardium at jeopardy. The results of some investigations, involving patients undergoing angioplasty, have suggested that individuals with both symptomatic and asymptomatic ischemia do not have larger amounts of myocardium at risk. Earlier work conducted by Deanfield and colleagues³ found no qualitative differences in perfusion abnormalities occurring in conjunction with painful and painless episodes in the same patient. Despite these findings, some observers continue to contend that the amount of jeopardized myocardium helps explain why some ischemic episodes are painful and some are not. Although the debate continues, its resolution may not be important from the standpoint of prognosis.

MECHANISMS OF MIXED ISCHEMIA

Our current state of knowledge would seem to support the view that most ischemia is mixed, involving mechanisms traditionally associated with specific types of angina. Moreover, the presence or absence of pain is not related to the cause of mixed ischemia; silent ischemia can occur in the setting of stable, unstable, or variant angina, despite differing pathophysiologic mechanisms.

Stable angina is usually considered to involve a fixed lesion, whereas unstable angina involves not only a fixed lesion but also components such as platelet aggregation, thrombotic processes, and vasospasm. Variant angina, by definition, involves primarily vasospasm. Mixed angina involves all these components at various times during the cycle of the patient's ischemic episodes.

Residual coronary flow reserve: Traditional concepts held that, in the presence of a fixed atherosclerotic obstruction, residual coronary flow reserve is fixed. In other words, residual coronary flow reserve is reduced to a moderate degree, so that myocardial perfusion is limited. Whereas a normal individual might increase coronary flow by

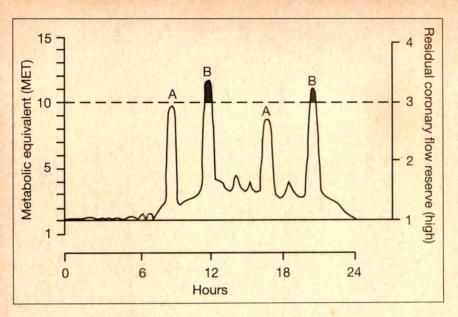


FIGURE 1. Traditional concept of fixed coronary flow reserve in the presence of fixed atherosclerotic obstruction. A = episodes not associated with ischemia; B = ischemic episodes: (---) = residual coronary flow reserve threshold. (Adapted with permission from J Am Coll Cardiol.4)

perhaps 4 times the level at rest in response to energy requirements, the patient with a fixed obstruction can increase flow only up to 3 times the level at rest, but no further (Figure 1).4 At a level of oxygen demand requiring greater flow, ischemia

The newer concept holds that residual coronary flow reserve is not fixed but rather varies over the course of a day in response to vasomotor changes (Figure 2).4 Although the residual coronary flow reserve still has an upper limit, it fluctuates in response to changes in resistance at the site of the flow-limiting stenoses. As a result, ischemic episodes continue to occur when exercise demands exceed the threshold of the residual coronary flow reserve, but ischemia also occurs at lower levels of energy consumption because the flow reserve is reduced. Ischemia can also occur at rest during episodes of intense vasoconstriction.

Morphologic progression during atherosclerosis: The concept of mixed ischemia also seems compatible with the morphologic progression of atherogenesis. With a fixed concentric lumen, there is basically no room for increased vasoconstriction, even during normal vasomotor changes that occur during the day (Figure 3).5 Although such changes may account for a small reduction in lumen diameter, few or no symptoms of ischemia may occur. Thus, in the presence of a markedly atherosclerotic region with a very small lumen, little additional vasoconstriction can occur during the day, and a patient with this morphology would likely experience ischemia only when myocardial oxygen demands reach a critical level.

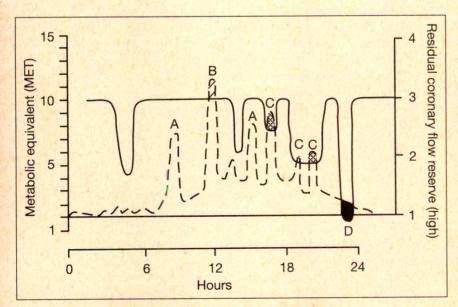


FIGURE 2. Concept of variable coronary flow reserve in presence of variable atherosclerotic obstruction. A = episodes not associated with ischemia; B = ischemic episode occurring at levels of exercise exceeding threshold of residual coronary flow reserve; C = ischemic episodes occurring at lower levels of exercise when residual coronary flow is reduced; D = ischemic episodes occurring at rest in presence of maximal reduction in residual coronary flow reserve; (---) = residual coronary flow reserve threshold; (---) = variable atherosclerotic obstruction, as measured by MET. (Adapted with permission from J Am Coll Cardiol.4)

On the other hand, with a more eccentric lumen, one containing areas where effects of vaso-constriction are possible, further reduction in lumen diameter can precipitate ischemia both at rest and on exertion (Figure 3). Finally, in the presence of large areas that are not severely compromised but have potential for marked vasoconstriction, ischemia may occur at rest.

CLINICAL FEATURES OF MIXED ISCHEMIA

The concept of mixed ischemia has been validated on the clinical level as well. In a survey of 110 consecutive patients with the diagnosis of stable angina, Nesto et al⁶ found that symptoms of mixed angina were common in most individuals. Some patients were experiencing anginal episodes under circumstances that would not typically be expected to provoke ischemia. The results suggest individual variation in the amount of vasoconstriction and responsiveness of the fixed lesion.

Another important element of this new level of understanding is the well-recognized circadian variation in both total ischemic activity and silent ischemic episodes. The majority of the ischemic episodes that occur during the day—as many as 75% in some studies—are not recognized by patients. Importantly, the circadian pattern of silent ischemia correlates with that associated with nonfatal myocardial infarction and sudden death. 7,8

These observations have prompted extensive research into potentially common mechanisms that may underlie these events and increase the risk of cardiovascular morbidity and mortality.

CONVERSION OF CHRONIC LESION TO ACTIVE LESION

The conversion of a chronic stenotic lesion to an active lesion can most likely be attributed to disruption in the luminal surface of an atherosclerotic plaque. The probable mechanisms of acute myocardial ischemia include rapid progression of atherosclerotic lesions, hemorrhage and rupture of the atheromatous plaque, subsequent formation of intravascular thrombus, and dynamic alterations in coronary tone. These alterations range from minor vasomotor changes to total spastic occlusion that may be caused, in part, by local platelet aggregation with the release of vasoactive substances.

Impairment of vascular endothelial function is an important precipitating factor. When the endothelium is damaged, disruption of normal hormonal balance and coagulation homeostasis may lead to thrombosis, spasm, or both. These events may occur independently or in combination as the disease progresses to acute ischemia. However, most events are mixed, resulting from atherosclerotic obstruction and coronary vasoconstriction.

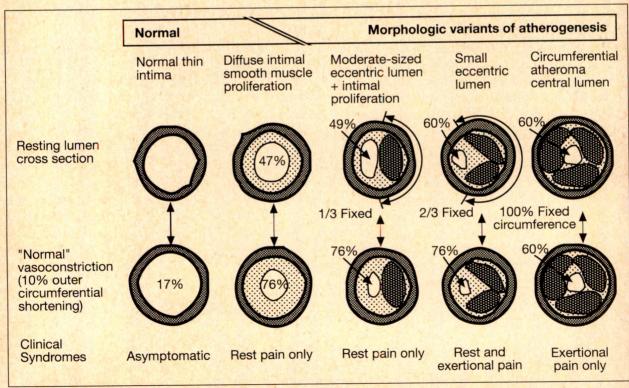


FIGURE 3. Morphologic progression during atherogenesis. (Adapted with permission from Arch Intern Med.5)

CONCLUSION

The traditional concept of myocardial ischemia as an imbalance in the supply and demand of myocardial oxygen is being modified by an improved understanding of the various mechanisms involved in the disease process. Newer concepts recognize the roles of both fixed lesions and vasomotor alterations in producing what is now termed mixed ischemia. Significantly, most ischemic events will not be perceived by patients, even though such events have adverse prognostic implications.

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DISCUSSION

Dr. William H. Frishman: Is transient myocardial ischemia a marker of disease, rather than the actual factor responsible for poor prognosis?

Dr. Peter F. Cohn: Ischemia is unquestionably a marker. However, the question of whether ischemia has deleterious effects that might be successfully treated remains unanswered. In one European study, surgical revascularization in patients with 3-vessel disease yielded no benefit over medical therapy with regard to prognosis if the individuals had negative exercise tests. Other work has shown that β blockers offer no advantage in terms of reducing the risk of mortality and in postinfarc-

tion patients with negative exercise tests. If the exercise test is positive, on the other hand, Bblocker therapy may offer benefit. However, we do not know whether this benefit accrues from an anti-ischemic effect or another mechanism, such as an antiarrhythmic, antiplatelet, or antiatherogenic effect.

Participant: Does ischemia have continuing effects on myocardial function? What are the potential long-term effects of recurrent ischemia?

Dr. Cohn: During the 1970s, studies conducted at Peter Bent Brigham Hospital in Boston found that apparently nonviable myocardium could be stimulated by a variety of agents, including epinephrine and postextrasystolic potentiation. These observations led to the concept of a chronic ischemic state, which has since been termed "hibernation." Therefore, I believe that repeated episodes of ischemia may lead to hemodynamic abnormalities in some situations. These abnormalities can be reversed by treatment of the ischemia. I do not believe at this time that we can extrapolate from these findings and conclude that repeated ischemic episodes will lead to a true cardiomyopathic state, although this is theoretically possible. I do, however, believe that these episodes lead to a myocardial state akin to what used to be termed "chronic" ischemia.

Participant: Why are diabetic patients more prone to nonrecognition of anginal pain? Is this characteristic related to the state of diabetic control?

Dr. Cohn: The lack of perception of anginal pain among diabetic patients seems to be most related to autonomic dysfunction. Patients with greater degrees of parasympathetic autonomic dysfunction seem more likely to have diminished pain perception. We do not know whether this is related to hyperglycemic control. Patients with diabetes can develop a cardiomyopathy that is not only a small vessel disease, as is most common, but that also involves large vessels in some cases. Therefore, it is possible that the lack of perception of anginal pain in individuals with diabetes can lead to repeated episodes of ischemia that can damage the ventricle.

New Insights in Measurement of Myocardial Ischemia

Carl J. Pepine, MD

Myocardial ischemia may be defined as myocellular dysfunction resulting from hypoxia usually due to limited coronary blood flow. The methods commonly used to make a diagnosis of myocardial ischemia employ either clinical findings (e.g., angina, myocardial infarction) or signals from laboratory tests. Since ischemia is often clinically silent and since clinical events related to ischemia may be catastrophic (i.e., myocardial infarction and sudden death), physicians are dependent on tests using various targeted signals. These signals, however, do not actually provide quantitative measurements of the degree of ischemia or related myocardial dysfunction. Nevertheless, the functional abnormalities reflected by these signals can identify patients at high or low risk for adverse outcomes related to ischemia. So, in this sense, these signals can be used to support the diagnosis of ischemia as well as evaluate its importance in a given patient. The most commonly used signal is an ST-segment shift evident on the electrocardiogram (ECG). When this is horizontal or downsloping and ≥1.0 mm, this is often, but not always, due to myocardial ischemia. Although assessment of the exercisestress ECG offers several advantages over assessment of the resting ECG, the standard Bruce protocol is associated with notable shortcomings that become apparent when an attempt is made to assess the effects of a treatment on the STsegment signal. These might be surmounted by use of a continuous ramp-type protocol. Ambulatory ECG monitoring is growing in importance in the wake of increasing awareness of the different daily life circumstances that are associated with ischemia. In addition, some differences have become noticeable when ischemia that occurs during exercise testing and ischemia that occurs

during daily activities are compared. Results of ambulatory ECG studies have underscored the importance of tailoring diagnostic procedures and therapies to the observed circadian variation in myocardial ischemia as well as to daily life experiences. Assessments of ischemia can also be based on a blood flow signal. The one most commonly used is a reversible perfusion defect detected with injection of certain radionuclides. Another signal is a reversible left ventricular regional wall-motion abnormality detected with radionuclide angiocardiography, echocardiography, or contrast angiography. At present the information gained from these studies is more important from the standpoint of risk stratification than as a guide to numerically accurate measurements of myocardial ischemia.

(Am J Cardiol 1992;70:19G-25G)

he diagnosis of myocardial ischemia depends in theory on the ability to detect and measure a specific marker of ischemia. By definition, an accurate and specific measurement would conform to a numerical standard and be free of error. Evaluated against these criteria, all the clinical methods used to "diagnose" myocardial ischemia have notable limitations.

LIMITATIONS OF TRADITIONAL APPROACHES

Clinical events such as angina, myocardial infarction, and sudden cardiac death may be used as indicators of myocardial ischemia. However, most ischemic episodes are clinically silent, and this limits the use of angina or myocardial infarction alone to make a diagnosis. Further, when clinically manifest, myocardial infarction and sudden cardiac death are catastrophic; therefore, some form of diagnostic testing for ischemia before such events occur is highly desirable.

To this end, coronary angiography has served as the reference standard against which diagnostic tests for myocardial ischemia have traditionally been compared. Unfortunately, coronary angiography can, at best, assess only the anatomy (e.g., size

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and shape) of the contrast-filled coronary artery lumen. This method clearly does not provide either a reliable physiologic or functional measurement of the adequacy of coronary blood flow, and it does not define either the presence or the absence of myocardial ischemia. Studies have shown that the growth of plaque is associated with atrophy of the adjacent media, so that plaque shifts outward instead of bulging inward.1 This contributes to dilation or "compensatory enlargement" of the atherosclerotic coronary artery.^{2,3} Recent studies

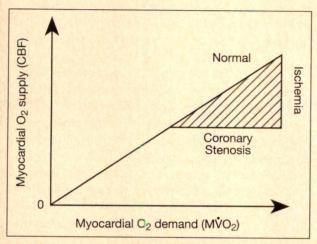


FIGURE 1. The normal myocardial oxygen supply-demand relationship and that seen with myocardial ischemia: As myocardial oxygen consumption is increasing (left to right on horizontal axis) in response to increasing demands such as those applied by exercise, the limitation in blood supply caused by coronary stenosis is exposed, and ischemia results. $CBF = coronary blood flow; MVO_2 = myocar$ dial oxygen consumption.

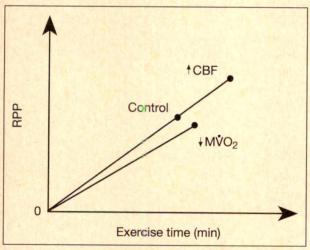


FIGURE 2. The response to anti-ischemic treatments, in theory, can be assessed from the index of myocardial oxygen demand (rate-pressure product [RPP]) and exercise time. If exercise time increases with an increase in RPP. then an improvement in coronary blood flow is likely. If exercise time increases but RPP is reduced or changed, a decrease in myocardial oxygen demand is likely. MVO₂ = myocardial oxygen consumption; CBF = coronary blood flow.

have suggested that plaque area must exceed 40% of the original cross-sectional area of a vessel before this capacity to preserve lumen size is overcome.1 So the plaque must be extensive before the angiogram will reveal an indication of obstruction at any given site. Thus, the coronary angiogram provides a highly limited assessment of coronary atherosclerosis, in most cases because the threshold for detection is relatively high; at best, it indicates only whether obstruction may be present. More recently, other tests done during coronary angiography have shown considerable promise. These include acetylcholine stimulation, as a test for endothelial dysfunction; intravascular ultrasound to measure lumen size, wall thickness, and plaque composition; and intravascular Doppler blood flow velocity to measure the maximal flow response during vasodilation. These tests, however, still do not measure ischemia per se.

Myocardial ischemia clearly involves more than simply epicardial coronary artery stenosis detected by angiography or intravascular ultrasound. The coronary artery is a continuously functional organ, and its diameter, as well as the diameter of its distal arterioles, changes in relation to a variety of mental and physical stressors and other evocative factors. As a result of these limitations, the role of tests often used to "measure" myocardial ischemia has changed in recent years. Because these tests do not actually measure ischemia, however, this role has been shifting in emphasis from a diagnostic to prognostic use.

Tests for myocardial ischemia must take advantage of the physiologic relationship between myocardial oxygen supply and demand. In most instances, this relationship does not result in ischemia when a patient is examined in either the office or at rest in a laboratory setting. However, if a tool (e.g., stress during exercise) is used to increase myocardial oxygen demand and produce ischemia in the laboratory, the dysfunction that results as the limitation in coronary blood flow (imposed by the diseased coronary obstruction) is exposed can be detected (Figure 1). The dysfunction thus detected can then be measured and used to obtain an index of ischemia. Similarly, the effects of potential anti-ischemic therapies can be assessed by comparing responses (e.g., to stress during exercise) before and after treatment. The information obtained can also be used to gain insight into the possible mechanisms by which a therapy may improve the response (e.g., exercise duration; Figure 2) before the onset of ischemic dysfunction.

CASCADE OF ISCHEMIA-RELATED EVENTS

An imbalance in myocardial supply and demand evokes a cascade of biochemical and mechanical changes within the myocardial segment jeopardized by the regional limitation in blood flow (Figure 1). These changes include inappropriate reduction in blood flow to the subendocardial region of the jeopardized segment. This limitation in blood flow causes changes that are translated to a functional signal, most often assessed by the ECG. Notably, however, the surface ECG is relatively insensitive to such ischemia-related changes. Recent studies using epicardial ECGs obtained at the time of coronary artery occlusion as a result of balloon inflation during angioplasty show ST shifts when the surface ECG does not.4 Radionuclide perfusion studies and wall-motion studies may show ischemia-related abnormalities when the surface ECG remains unchanged.

The evolution of an ischemic episode, as described before in physiologic terms, leads to any of 4 possible clinical outcomes, the most common of which is resolution of the ischemic episode without the patient perceiving its occurrence (about 70-80% of all episodes are silent). The next most common outcome is the perception of chest discomfort (i.e., angina or one of its equivalents). Myocardial infarction occurs less often, and ventricular arrhythmias and sudden death are infrequent. From the foregoing it is apparent that some laboratory signal, other than the actual clinical outcome, is highly desirable as a surrogate for the presence of ischemia, and it may confirm the diagnosis.

SIGNALS OF MYOCARDIAL ISCHEMIA

In general, 1 of 3 methods are employed to assess the presence of myocardial ischemia in the clinical setting. The most frequently used method employs an ECG signal, usually ST-segment shifts, which are often-but not always-associated with myocardial ischemia. Other approaches involve the detection of a regional blood flow signal (usually a reversible perfusion defect) or a left ventricular regional wall-motion signal (most commonly, reversible wall-motion abnormalities).

Electrocardiographic signal: The resting 12lead ECG recording is important in the evaluation of ischemia. Findings of old myocardial infarction (e.g., Q waves) indicate that severe ischemia must have been present in the past. Current ischemia cannot be inferred unless serial tracings reveal transient ST-segment shifts, which are ≥1.0 mm depression or ≥ 2.0 mm elevation, in the absence of other causes. Other types of ECG recordings are

TABLE I Visual Monitoring of the Electrocardiogram (ECG) in the Coronary Care Unit Is Not Adequate to Detect Ischemia

Analysis Condition	Ischemic Episodes Identified (≥2.0-mm ST-segment change)	
	n	%
Retrospective tape analysis	213	100
Nursing staff—real time	31	15
Cardiologist—real time		
Presented with 4 ECG tracings	102	48
Presented with only 1 ECG tracing	196	92

critical care unit monitoring and telemetry. Many of the ECG systems used in these areas do not have adequate fidelity to allow reliable reproduction of the ST segment. Biagini et al⁵ recorded the ECG in patients from the coronary care unit and then examined the results of analyses done retrospectively versus in real time (Table I). Even when the signal fidelity is adequate, careful visual observation in real time by a cardiologist is very limited in the identification of transient abnormalities that are thought to be related to ischemia.

In view of these and other shortcomings, treadmill testing in the exercise laboratory is most commonly used to assess patients for the presence of myocardial ischemia. The treadmill test is an evocative stress used to increase myocardial oxygen demand in stages. The patient is asked to increase the level of external work so that myocardial oxygen demand, as reflected in the rate-pressure product, increases. Over the past 20 years or so, the Bruce protocol has evolved as the standard testing method in most laboratories in the United States. This protocol is excellent for detecting ischemiarelated abnormalities in large populations (e.g., screening). The response to exercise also can be used to infer the possible mechanism by which an intervention relieves or prevents ischemia (Figure 2). Many observers believe, however, that this protocol is probably not the most appropriate test to use for serial testing in order to assess the effects of an intervention in patients with coronary artery disease and ischemia.

The Bruce protocol increases metabolic equivalents (METs) in relatively steep steps (e.g., approximately 3 METs; Figure 3). By practical limitation, the patient does not usually achieve hemodynamic stabilization when exercise duration at a given level is <3 minutes. Relatively few patients with symptoms of ischemic heart disease exercise for > 9-10 minutes using the Bruce protocol. Therefore, the difference between stages 2 (from the 4th to the end of the 6th minute) and 3 (from the 7th to the

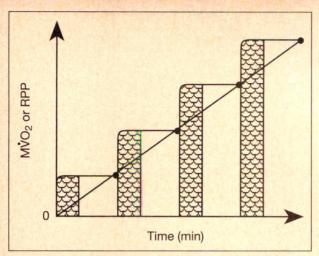


FIGURE 3. The hypothetical myocardial oxygen consumption response to increasing levels of treadmill exercise stress. This example illustrates expected responses to the Bruce protocol in which 1 stage represents about 3 metabolic equivalents [METS]. RPP = rate-pressure product; MVO₂ = myocardial oxygen consumption.

end of the 9th minute) of the Bruce protocol is usually measured. Because the protocol has abrupt steps, ischemia is evoked at or shortly after the time that the level is changed from stage 1 to 2 or from stage 2 to 3. Thus, what should, in theory, be a continuous variable (e.g., exercise time) actually becomes a discrete variable, because the onset of ischemia is forced into a cluster of time about the stage change. So this abruptly stepped protocol is limited when repeated testing is desirable for follow-up or evaluation of the efficacy of antiischemic therapy. This fact accounts for the repeated observation that clinically apparently effective drug treatment results in very limited increases in exercise time (e.g., about 30-50 seconds) when the Bruce protocol is used. Ideally, a continuous ramp-type protocol should be most helpful to spread out the differences in exercise time that may exist when smaller increments in myocardial oxygen demand are used. This would also more closely simulate daily life.

Several nonexercise forms of stress testing have also evolved. Atrial pacing as a form of tachycardia stress has fallen out of favor in recent years but remains useful for the occasional patient who is unable to exercise. Catecholamine infusion and cold pressor testing are likewise used less often than in the past, probably because these approaches are time-consuming and have a relatively low yield compared with exercise testing.

More recently, greater attention has focused on the link between myocardial ischemia and psychophysiologic evocative factors present in the patient's everyday environment. These so-called mental or psychologic stressors will probably be used in a more structured fashion in the future to evaluate myocardial ischemia.

Ambulatory ECG monitoring is being used increasingly to identify ischemia during daily activities. In a study of totally asymptomatic individuals with severe coronary artery disease, ambulatory ECGs showed episodes of marked ST-segment depression during daily activity at heart rates well below those seen during ST-segment depression on exercise treadmill testing.⁶ These observations are the same as those made by us a number of years

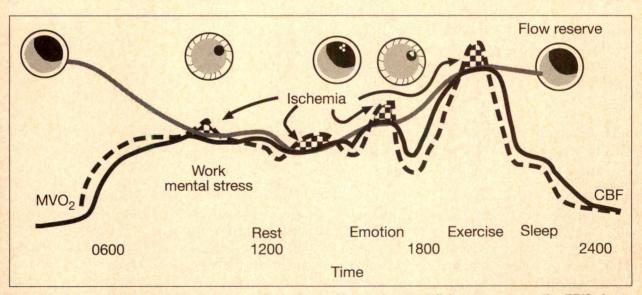


FIGURE 4. A revised concept of transient myocardial ischemia. Changes in myocardial oxygen consumption (MVO2; broken line), and coronary blood flow (CBF; heavy line) are shown throughout the day for various daily activities. The CBF reserve ceiling (gray line) is variable, dependent on vasoconstriction, platelet aggregation, and other dynamic factors operating in a given patient at a given time. As a result, ischemia (shown as shaded areas where MVO2 exceeds CBF) occurs often during the day. (Adapted with permission from Cardiovasc Clin. 10)

ago in patients with angina undergoing ambulatory ECG monitoring. This indicates that most patients with ischemia (either symptomatic or asymptomatic) have their ischemic episodes during daily life at lower indices of myocardial oxygen demand than those associated with the ischemic episodes that occur during exercise testing.

Several explanations have been proposed for the occurrence of ischemia at lower heart rates during daily activities. Some observers have suggested that the relationship between myocardial oxygen supply and demand must be influenced by factors (i.e., reduced coronary blood flow) in daily life that lower the ischemic threshold. As a result, a revised concept of transient myocardial ischemia has evolved in which the ischemic threshold of any patient varies relative to oscillations in coronary flow reserve that occur in a circadian fashion throughout the day (Figure 4). The coronary flow reserve changes in relation to circulating levels of catechols, adrenergic activation, and most likely a host of other factors that remain to be identified possibly platelet aggregation, smooth muscle activation, or transient endothelial dysfunction. Another important consideration is myocardial oxygen demand, which increases when the patient awakens in the morning and may exhibit subsequent, additional increases in response to external work stress, mental stress, emotional states, and exercise.

The diurnal variation in myocardial ischemia has been well documented within the past few years. Characteristically, ischemia increases within 1–2 hours after the patient awakens, peaks between about noon and 2 P.M., then declines slowly

throughout the remainder of the day. Some debate has centered on the question whether a secondary peak occurs during the very late afternoon and early evening or whether the observed changes in some patients are simply manifestations of a lower rate of decline of the peak activity. Although a small minority of patients have nocturnal ischemia, the level of ischemic activity usually remains low during the hours of sleep.

Any tool used to diagnose myocardial ischemia should take advantage of this circadian variation. It would be most fruitful to attempt to detect ischemia during the peak hours. Correspondingly, therapeutic regimens should be tailored so that the effects of anti-ischemic drugs are optimal during this time.

Endothelial dysfunction may be an important factor in the pathogenesis of ischemia experienced during daily activities. Clearly, damage to the coronary artery endothelium seems to precede the cascade of events leading to ischemia in daily life. The endothelium then becomes mechanically, biochemically, and physiologically dysfunctional. These changes result in lesser degrees of coronary dilation and even inappropriate constriction and loss of metabolic function, leading to a destabilized plaque, an increased tendency toward plaque rupture or disruption, and an increased risk of intramural hemorrhage, mural thrombus, and occlusive thrombus.

Psychophysiologic stress is a notable feature of the relationship between myocardial ischemia and the patient's daily environment. This association has long been recognized and was recently illus-

FIGURE 5. The effect of the 1991 iraqi missile attacks on the incidence of acute myocardial infarction (MI) among israeli civilians. Note the increase in MIs during January 8–25, 1991, compared with MIs during January 8–25, 1990. (Adapted with permission from Lancet.⁷)

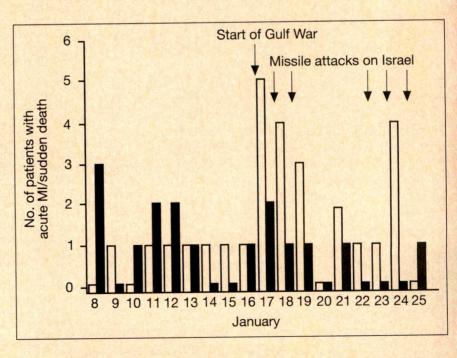


TABLE II Accuracy of Exercise Electrocardiogram (ECG) and Thallium-201 Scintigraphy Results in Predicting Coronary **Events in Asymptomatic Patients**

	Results (%)		
Descriptor	ECG	Thallium-201	Concordant Positive*
Sensitivity	40	30	28
Specificity	86	88	97
Positive predictive value	24	22	48
Negative predictive value	93	92	92

*Any combination of ECG and thallium-201 findings other than positivity on both ests is considered a negative result.

Adapted with permission from Circulation.8

trated by a report from a Tel Aviv hospital where the incidence of myocardial infarction and sudden death among Israeli civilians was noted to have increased 2- to 3-fold at the times of Iraqi missile attacks during the 1991 war in the Persian Gulf (Figure 5).7

Blood flow signal: The assessment of myocardial ischemia can also move away from the ECG and analysis of endpoints such as myocardial infarction toward assessments based on a blood flow signal. Thallium-201 perfusion scans can be done during a variety of stresses. The use of dipyridamole-stress thallium-201 perfusion testing is popular. Recently, this may have decreased in response to the widespread availability of adenosine, which is now a common pharmacologic "stress" agent used in the laboratory evaluation of patients with suspected myocardial ischemia. The assessments can take the form of either planar or single photon emission computed tomographic (SPECT) studies. The newer technetium-99m imaging agents can be used both at rest and during stress testing, as can positron emission tomography (PET). A recent report has shown that the sensitivity of the thallium signal is extremely low, compared with the exercise ECG signal, in totally asymptomatic but high-risk individuals. However, the negative predictive value of thallium-201 scintigraphy is extremely high (Table II).8 This noninvasive study therefore offers high specificity when combined with the exercise ECG signal for the exclusion of patients with important coronary artery obstruction and ischemia, but it remains relatively insensitive in the detection of those who may experience ischemic

Left ventricular wall-motion signal: Another modality used for assessing myocardial ischemia involves detection of the left ventricular regional wall-motion signal. This can be determined by radionuclide ventriculography performed at rest and during stress. Most often, this is done from an

analysis using the multiple equilibrium-gated image acquisition method during a technetium-99m pertechnetate study. The other method used is the first-pass technique. Echocardiography is increasingly used to detect regional wall-motion abnormalities at rest and during stress in order to evaluate ischemia. Dobutamine stress echocardiography has recently attracted attention.4 Another time-honored method for left ventricular wall-motion analysis that may be used at rest and during stress is contrast angiography. Here, the response to nitroglycerin can be used as an indication of relief of ischemia-related dysfunction.9

CONCLUSION

The methods now used to support the diagnosis of myocardial ischemia assume that the targeted signals can serve as measurements of ischemia. In the true sense, however, none of these approaches actually measures myocardial ischemia, and the findings cannot be precisely quantified. Nonetheless, the functional abnormalities identified by these techniques can be used for classification of patients into high- and low-risk subgroups. In a sense, then, these tests help to support the diagnosis of ischemia rather than make the diagnosis itself. At this time, it is more important to obtain these measurements for the purpose of stratifying risk and determining prognosis than to attempt to measure ischemia with numerical accuracy.

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DISCUSSION

Dr. William H. Frishman: If a patient has a positive electrocardiographic (ECG) response to exercise, without pain, and is in a high-risk category, what test should be performed next?

Dr. Carl J. Pepine: In our institution, we usually proceed to coronary angiography, but the individual characteristics must be considered. Coronary angiography might not be advisable in an 80-yearold patient, for instance, although no precise age limits should be set. In general, however, if the stress test indicates the presence of high risk, regardless of symptoms, a definitive test is needed to exclude the presence of severe coronary artery disease, such as left main or 3-vessel obstruction.

Participant: Traditionally, the time to ischemia on exercise testing has been used as a method of evaluating the efficacy of pharmacologic therapy in the prevention or treatment of the disorder. Sometimes, even a 30-40-second increase in exercise time is cited as evidence of a prominent antiischemic effect of a medication. Can one expect this effect to be reproducible in the chronic situation, in light of the host of factors that influence the time to ischemia?

Dr. Pepine: Many studies of antianginal agents have used patients who were able to perform 2 exercise tests in which the difference in durations was within 10-15%. The reason for 10-15% is difficult to determine. Unfortunately, only an extremely small subset of patients with abnormal exercise test responses and coronary artery disease have reproducible (within 15%) exercise tests. This is one of the reasons I have advocated revising the standard exercise (Bruce) protocol to eliminate abrupt increases in METs and, I hope, produce more reproducible tests. Also, there are numerous environmental and psychophysiologic factors operative in these patients, and it may be unrealistic to expect any exercise protocol to control for variability caused by all of these factors.

Treatment of Chronic Stable Angina Pectoris

Richard Gorlin, MD

Patients with angina pectoris may be stratified into low- or high-risk categories on the basis of clinical findings and a careful workup, possibly including nuclear imaging of stress-induced abnormal perfusion or contractile patterns and coronary angiography. High-risk patients may require revascularization by angioplasty or bypass surgery, whereas low-risk patients can be managed medically. It is important to consider the impact of various anti-ischemic drugs on the myocardial demand-supply equation. A recent study indicated that the combination of a β blocker plus isosorbide mononitrate is more effective in increasing exercise duration than is either the combination of a B blocker and a calcium antagonist or triple therapy. In patients with single-vessel disease, angioplasty has been shown to be more effective than medical therapy in relieving symptoms, but the incidence of restenosis and the associated costs are high. Surgery favorably affects mortality in patients with left main coronary artery disease or 3-vessel disease with left ventricular impairment. New evidence suggests that endothelial dysfunction may play a more important role in chronic stable angina pectoris than has been appreciated and that such dysfunction may be treated with nitrates.

(Am J Cardiol 1992;70:26G-31G)

he key to therapeutic decision-making in chronic stable angina pectoris is risk stratification (Figure 1). Management begins with identification of factors that may precipitate or exacerbate myocardial ischemia by increasing myocardial oxygen demand, including, but not limited to, obesity, smoking, hypertension, anemia, and thyrotoxicosis. The presence or absence on noninvasive testing of such signs as ST-T changes at a low level of exercise, inappropriate blood pressureheart rate responses to exercise, large or multiple transient perfusion deficits, or left ventricular (LV) dysfunction helps to distinguish low-risk patients, who should most often receive medical therapy, from high-risk patients, who should undergo coronary angiography. Coronary angiography permits delineation of the subset of patients who are candidates for revascularization by percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting. In the absence of such high-risk angiographic findings as left main coronary artery disease (CAD) or 3-vessel disease (especially with LV dysfunction), a trial of medical therapy is indicated. As shown in the algorithm in Figure 1, if medical treatment fails or is not tolerated, revascularization must be considered; conversely, if the patient becomes symptomatic following revascularization, medical therapy again becomes an option.

MEDICAL THERAPY

An imbalance between myocardial energy demands and coronary flow will give rise to the metabolic, electrophysiologic, and mechanical aberrations that culminate in ischemia. When selecting a therapeutic intervention for the patient with angina, a key consideration is how that intervention will affect the determinants of demand (cardiac contractility, heart rate, and wall stress) on the one hand and the determinants of supply (perfusion pressure and coronary vascular resistance) on the other.

Mechanisms of action: Nitrates, β blockers, and calcium antagonists represent the cornerstone of medical therapy for angina pectoris. The nitrates are unique as vasodilators in that they not

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only dilate the arteries and arterioles, but also selectively induce venous dilation. The effects on large arteries are most profound in the coronary vessels, especially at sites of stenosis. Nitrates decrease myocardial oxygen demand primarily by diminishing preload. In addition, nitrates exert mild secondary effects on contractility and heart rate via stimulation of the sympathetic nervous system, concomitant with a fall in blood pressure. Beta blockers act by reducing contractility, heart rate, and blood pressure, particularly in response to any sympathetically modulated stress, and to some extent by redistributing blood flow across the myocardial wall. Calcium antagonists exert a profound vasodilatory effect on both peripheral and coronary resistance vessels and, in the process, reduce afterload.

Optimizing therapy: Successful antianginal therapy depends on objective measurement of drug activity, coupled with selection of a dose, route of administration, and dosing interval that will maximize efficacy and patient convenience and minimize adverse effects and tolerance.

With nitrates, for example, measuring the patient's blood pressure should indicate whether adequate vasodilation has been achieved. However, attention to the dosing interval is particularly important to avoid the development of tolerance.

With β blockers, a decrease in heart rate is the simplest marker of drug activity. It is interesting to note that, during β blockade, cardiac output and heart rate do rise in response to exercise but usually to a level below that achieved without β blockade. In patients who experience side effects with β blockade, the severity of the reaction must be weighed against the cardioprotective actions of these agents.

Since the blood pressure response to calcium antagonists may be muted, recognition of activity can be difficult unless a patient was originally hypertensive or develops orthostatic hypotension. Dosing convenience had been a problem with these agents until recently, when many sustained release preparations became available.

Combination therapy: Since some anti-ischemic agents may have complementary modes of action, combination therapy may be useful in relieving ischemia and pain. However, current strategies emphasize that double therapy is often as effective as triple therapy.

In a recent double-blind crossover trial by Akhras and Jackson,² patients with stable angina pectoris were randomized to receive atenolol alone, atenolol plus nifedipine, atenolol plus isosorbide mononitrate, or all 3 drugs. The number of angina attacks and consumption of nitroglycerin were

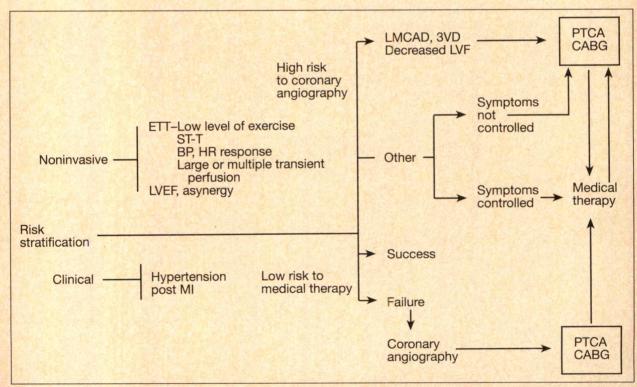


FIGURE 1. Algorithm for therapeutic decision making in patients with coronary artery disease. BP = blood pressure; CABG = coronary artery bypass grafting; ETT = exercise tolerance test; HR = heart rate; LMCAD = left main coronary artery disease; LVEF = left ventricular ejection fraction; LVF = left ventricular failure; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; 3VD = 3-vessel disease.

comparable with all 4 regimens. The study's only significant finding was a longer duration of exercise in patients who received the β blocker plus isosorbide mononitrate compared with patients taking the B blocker alone or with the calcium antagonist. Triple therapy conferred no advantage with regard to either exercise testing or clinical effects.

Our approach is to treat stable angina pectoris patients with combination therapy comprising a B blocker and a vasodilator. The B blocker is prescribed for its salutary hemodynamic and cardioprotective actions. A nitrate vasodilator is preferable, both for empirical reasons and because the nitrates cause release of nitric oxide, which enhances the impaired coronary vasodilator response seen in the presence of atherosclerosis.

REVASCULARIZATION

If medical treatment is ineffective or is not tolerated, revascularization by PTCA or bypass grafting must be considered.

Angioplasty: Although angioplasty allows revascularization to be achieved nonsurgically, a major drawback is the high rate of restenosis following the procedure. Angioplasty is initially successful in approximately 87% of patients. Within a year, however, nearly a third of these patients will require a second procedure, the success rate of which is closer to 70%. Thus, the overall outcome is satisfactory in about 80% of patients 1 year after angioplasty.3

Until recently, it was unclear whether patients with single-vessel disease and stable angina pectoris benefited more from medical therapy or from

angioplasty. The Veterans Affairs' Angioplasty Compared to Medicine (ACME) study has just shown that PTCA is somewhat more effective in relieving angina and improving exercise performance in patients who have exercise-induced ischemia and > 70% stenosis of 1 epicardial artery. 4 Six months after random assignment to angioplasty or medical therapy, 64% of the patients who underwent angioplasty were free of symptoms, compared with 46% of patients in the medical therapy group (Figure 2). PTCA increased the total duration of exercise by > 2 minutes, whereas medical therapy increased it by only 0.5 minute. Patients in the PTCA group were able to exercise significantly longer without developing angina than were medically treated patients. Moreover, patients who underwent angioplasty experienced 15 fewer angina attacks per month, compared with a decrease of only 7 attacks per month in the medical therapy group. Myocardial infarction occurred in 5 patients assigned to PTCA and in 3 with medical therapy. However, PTCA was successful in only 80 of the patients. Two of these represent emergency bypass surgery, 16 represent repeat PTCA. PTCA also proved to be the more costly of the 2 treatment approaches because of the need for emergency coronary artery bypass surgery and because of the incidence of repeat dilation following restenosis. Employment status was not altered.

Surgery: If an overall reduction in mortality is a goal of management of coronary artery disease, then patients must be substratified before an appropriate therapy can be selected. For example, there is no doubt that surgery improves survival in

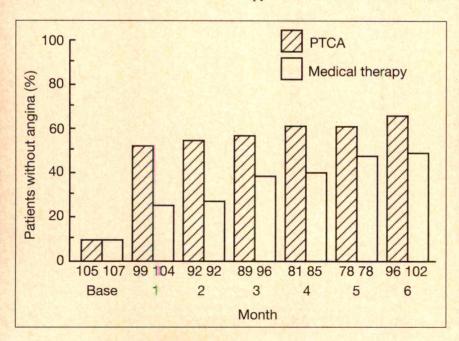


FIGURE 2. Percentage of patients free of angina each month after randomization to percutaneous transluminal coronary angioplasty (PTCA) or medical therapy for single-vessel coronary artery disease in the Veterans Affairs **ACME trial. Numbers below bars** are number of patients evaluated. Base = baseline. (Adapted with permission from N Engl J Med.4)

patients with left main CAD, where the obstruction jeopardizes virtually the entire left ventricle. It was shown almost 2 decades ago that 42-month survival is nearly 90% in surgically treated patients with left main disease but only 30% in their medically treated counterparts.⁵

The Coronary Artery Surgery Study (CASS), a randomized trial of 780 patients, demonstrated comparable 5-year survival rates with medical and surgical therapy in patients with stable ischemic heart disease. However, in patients with a subnormal ejection fraction (<50%), surgery proved superior to medical therapy in prolonging life (Figure 3).6 When the CASS investigators analyzed quality of life rather than survival, they found that surgery relieved pain and improved functional status better than medical therapy but had no effect on employment status.⁷

In contrast, the European Coronary Surgery Study group⁸ concluded that surgery was the treatment of choice in patients with good LV function and either 3-vessel disease or stenosis of the proximal third of the left anterior descending artery. According to the results of this prospective randomized trial, independent predictors of a better outcome with surgery were such risk factors as an abnormal resting electrocardiogram, ≥ 1.5 mm ST-segment depression during exercise, and the presence of concomitant peripheral arterial disease. The European investigators recommended that patients with these risk factors undergo surgery even if angina responds satisfactorily to medical therapy.

It should be noted that only about 60% of saphenous vein grafts remain patent 10–12 years after surgery. Graft patency rates have been re-

ported to decrease within the first year following surgery, then to remain relatively constant until years 5–7, after which time another drop in patency rate can be documented. Although atherosclerosis progressed in all native coronary arteries, the rate of progression was greater in arteries with occluded grafts than in coronary arteries either with patent grafts or without any grafts. Progression of atherosclerosis has generally been found to be associated with deterioration in LV function as well.

LV function also has a significant impact on long-term survival after coronary bypass surgery, both with and without internal mammary artery grafting. In patients who underwent internal mammary artery grafting, 10-year survival was 88% in patients with good LV function but only 77% in patients with poor LV function. In patients who did not undergo internal mammary artery grafting, 10-year survival was 79% in patients with no or mild LV impairment but plummeted to 60% in those with moderate or severe impairment. 10

Many patients who undergo surgery ultimately return to medical therapy. In the European Coronary Surgery Study, the proportion of surgically treated patients taking β blockers increased from 20% 1 year after surgery to approximately 37% after 5 years.⁸ Parallel changes in the need for nitrate treatment were observed over 5 years of follow-up. These data, taken together with similar findings from the CASS study,⁷ indicate that, over the long term, combination medical therapy becomes the rule in bypass surgery patients.

To summarize the indications for surgical therapy, surgery may favorably affect the prognosis in patients with left main CAD, 3-vessel disease,

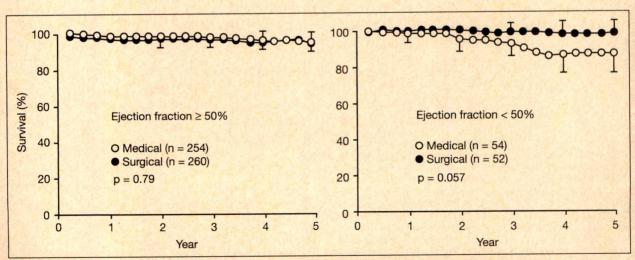


FIGURE 3. Ejection fraction and 5-year cumulative survival in patients with mild-to-moderate angina in the medical and surgical subgroups of the Coronary Artery Surgery Study (CASS). (Adapted with permission from Circulation.⁶)

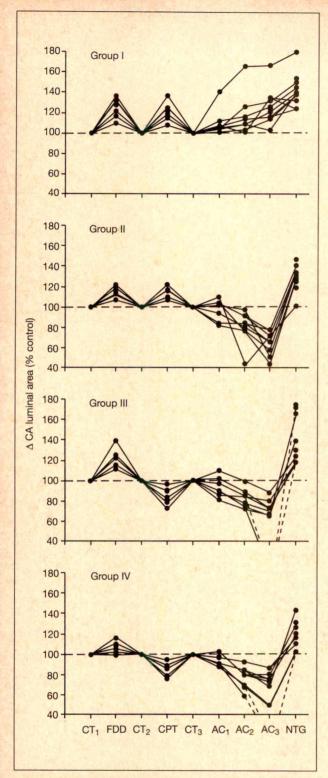


FIGURE 4. Change from baseline values (CT1, CT2, CT3) in coronary artery (CA) luminal area in response to increased blood flow (flow-dependent dilation [FDD]), cold pressor testing (CPT), increasing concentrations of acetylcholine (AC1, 10⁻⁸ M; AC2, 10⁻⁷ M; AC3, 10⁻⁶ M), and nitroglycerin (NTG). Group I = smooth coronary arteries plus absence of risk factors for coronary artery disease, plus hypercholesterolemia (group II), or plus evidence of atherosclerosis elsewhere in the coronary system (group III). Group IV = angiographic evidence of coronary artery wall irregularities. (Adapted with permission from Circulation.11)

especially with impaired LV function, or if medical therapy is ineffective or not tolerated.

ROLE OF ENDOTHELIAL DYSFUNCTION IN CHRONIC STABLE ANGINA

Endothelial dysfunction may play a more important role in chronic stable angina than has been appreciated. New evidence suggests that measurable abnormalities in endothelial vasoactive function may precede the development of angiographically detectable atherosclerotic lesions (Figure 4). According to a recent report, the coronary vasodilator response to 3 different endothelium-mediated stimuli (intracoronary acetylcholine, increased blood flow to induce flow-dependent dilation, and sympathetic stimulation by cold pressor testing) differed in patients with different stages of atherosclerosis. 11 Subjects with normal coronary arteries and no risk factors (group I) showed vasodilation in response to all 3 stimuli, whereas those who had angiographically normal coronary arteries but were hypercholesterolemic (group II) showed a vasoconstrictor response to acetylcholine (Figure 4). Smooth coronary artery segments in patients with evidence of disease elsewhere in the coronary system dilated with increased flow but constricted in response to acetylcholine and cold pressor testing, whereas coronary artery segments with luminal irregularities constricted in response to all 3 endothelium-dependent vasodilator stimuli. Nitroglycerin, which acts directly on vascular smooth muscle, induced dilation in all of these coronary segments, regardless of the stage of atherosclerosis (Figure 4). These findings suggest the potential utility of the nitrates in compensating for dysfunctional endothelium in atherosclerosis, and perhaps even in patients with hypercholesterolemia.

CONCLUSION

Medical therapy represents the preferred treatment strategy for low-risk patients with chronic stable angina. In addition, a sizable proportion of patients who undergo revascularization by PTCA or bypass grafting eventually return to medical therapy. With combination therapy, complementary drug actions can be harnessed to relieve pain and ischemia. The most advantageous combination would appear to be a \beta blocker, for its hemodynamic and cardioprotective actions, coupled with a nitrate, for its multilevel vasodilating actions, and for its ability to compensate for endothelial dysfunction.

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DISCUSSION

Participant: As a family physician, I am interested in your views on nonpharmacologic approaches to the treatment of stable angina pectoris, utilizing stress management, nutritional counseling, and an appropriate exercise program.

Dr. Richard Gorlin: I think these approaches are

all important. Nutritional counseling to reduce low-density lipoprotein levels may be desirable, although I would be curious to see the actual results obtained with such counseling. I advocate eating fish and perhaps even taking fish oil, since Selwyn's group has shown that fish oil can reverse endothelial dysfunction. The evidence is also quite clear that mental stress can reduce the caliber of the coronary arteries in patients with established coronary disease. Thus, stress modification is extremely important, if it can be achieved. The dangers of smoking are so great and so well recognized that it is hardly necessary to discuss the importance of stopping. Some authorities believe that a regular exercise program is helpful, but the most important aspect, I believe, is for the patient to remain physically active. One way to achieve this is through planned walking 3-4 times a week.

Participant: You discussed the effects of B blockade on the heart rate and cardiac output responses to exercise. Is it necessary to discontinue a β blocker before exercise testing?

Dr. Gorlin: If the purpose of the exercise test is to evaluate the efficacy of medical therapy, the test should be performed with the patient on therapy, preferably at the nadir of drug effect just before the patient is due to take the next dose. In contrast, an exercise test ordered for diagnostic reasons or for late assessment of surgical results should be performed with the patient off therapy. Gradual weaning from the B blocker is necessary to avoid the possibility of rebound.

Treatment of Unstable Angina Pectoris

Gary Gerstenblith, MD

Unstable angina pectoris may be manifested as new-onset angina, a change in the anginal pattern, pain at rest with associated electrocardiographic (ECG) changes, or postinfarction angina. Of these, pain at rest with ischemic ECG changes is known to be associated with the poorest prognosis. The pathogenesis of unstable angina pectoris involves a combination of a fixed atherosclerotic obstruction and a dynamic component related to coronary vasoconstriction, thrombus formation, or both. Long-acting nitrates, inhibitors of platelet aggregation, β blockers, and calcium antagonists are among the agents that have been shown to be effective in the medical management of unstable angina. A study now in progress is evaluating the routine use of thrombolytic therapy for this indication. Although alleviation of symptoms and prevention of death and myocardial infarction are important therapeutic goals, the overall efficacy of a particular medical therapy can best be assessed by objective evaluation of its ability to control ischemia, using such techniques as exercise scintigraphy and ambulatory ECG monitoring. Cardiac catheterization and revascularization are indicated for patients with unstable angina who continue to experience symptoms or who show evidence of silent ischemia despite medical therapy. A study is under way to determine the advisability of routine revascularization of such patients. Revascularization will provide symptomatic relief in most patients with unstable angina and may prolong survival and improve left ventricular function in certain subsets.

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nstable angina pectoris may be defined as new-onset angina, a change in the pattern of preexisting angina, pain at rest accompanied by ischemic electrocardiographic (ECG) changes, or postinfarction angina. Of these various forms, pain at rest with ECG changes is known to be associated with the poorest prognosis, as first noted by Gazes et al in 1973. In their 10-year follow-up study of 140 patients, those with prior stable angina who subsequently experienced rest pain with ECG changes during hospitalization had the highest mortality. Similar observations were later made by other investigators.

PATHOPHYSIOLOGIC FEATURES OF UNSTABLE **ANGINA PECTORIS**

In contrast to stable angina pectoris, which is attributable primarily to an increase in myocardial oxygen demand in the setting of a fixed atherosclerotic obstruction, unstable angina pectoris is most often characterized by dynamic coronary obstruction superimposed on a fixed atherosclerotic lesion. Cardiac catheterization studies of patients with unstable angina have demonstrated fixed atherosclerotic disease in > 90%. There is also substantial evidence to support the involvement of dynamic vasoconstrictive and thrombotic mechanisms that become activated following the fissuring or disruption of atherosclerotic plaque.

The role of coronary vasospasm in the pathogenesis of unstable angina is suggested by the findings of hemodynamic, ECG, and angiographic studies conducted by Maseri et al.² Transient vasospastic episodes may be caused by platelet-dependent or thrombin-dependent vasoconstriction precipitated by deep arterial damage or plaque disruption.³ Even mild endothelial dysfunction may lead to vasoconstriction by promoting the release by endothelial cells of physiologic mediators of vasoconstriction, such as endothelin-1, or inhibiting the release of vasorelaxant factors, such as prostacyclin and endothelium-derived relaxing factor.

Intraluminal thrombus formation resulting from platelet adhesion and aggregation at the site of plaque disruption is another important factor in the pathogenesis of unstable angina. Platelet aggre-

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gation is known to be enhanced by certain systemic factors, such as elevated circulating catecholamine levels, hypercholesterolemia, and impaired fibrinolysis, which may be manifested by increased serum concentrations of lipoprotein(a) and plasminogen activator inhibitor type 1. Evidence for the involvement of this latter factor is provided by the findings of Zalewski et al,4 who compared fibrinolytic activity in patients with unstable angina with that in patients with stable exertional angina and control subjects with normal coronary arteries. Although tissue-type plasminogen activator activity was comparable in the 3 groups, plasminogen activator inhibitor type 1 activity was significantly higher in patients with unstable angina than in those with stable angina or controls (Figure 1).

MEDICAL THERAPY FOR UNSTABLE ANGINA PECTORIS

Initial steps in the acute medical management of patients with unstable angina pectoris include admission to the coronary care unit, recognition and reversal of any precipitating factors (such as anemia, fever, and arrhythmias), and institution of full anticoagulation. The efficacy of heparin in the management of unstable angina was documented in a randomized, double-blind, placebo-controlled study published by Théroux et al in 1988.⁵ The 118 patients with acute unstable angina who were randomly assigned to receive 1,000 U/hr of intravenous heparin had a significantly lower incidence of myocardial infarction (MI) and refractory angina than the 118 who received placebo. The 121 patients treated with aspirin 325 mg twice daily also had a significantly lower incidence of MI compared with those given placebo. The protective effect of the combination of aspirin and heparin in this patient population was no greater than that of heparin alone. A subsequent follow-up study showed a significant incidence of recurrent ischemia when heparin was withdrawn in those patients not receiving aspirin.6

A number of agents have been shown to be beneficial in the long-term management of unstable angina pectoris. Among these are nitrates, whose effectiveness in the treatment of unstable angina is well documented. Nitrates decrease myocardial oxygen demand by reducing both preload and afterload, improve myocardial oxygen supply, favor the redistribution of coronary flow to ischemic areas, and prevent vasoconstriction. Nitrates also possess antiplatelet activity and exert favorable effects on the coronary endothelium.

At one time, the role of B blockers in the

treatment of unstable angina pectoris was a controversial issue. Among the reasons for this controversy was a report by Robertson et al7 of the prolongation of anginal episodes in patients with pure vasotonic angina treated with propranolol alone, an effect possibly related to unopposed α-induced coronary vasoconstriction. Most patients with unstable angina, however, do not have pure vasotonic angina. Furthermore, β blockers are seldom used as monotherapy in these patients but are more likely to be added to a regimen that also includes nitrates and calcium antagonists. When used in such combination therapy, B blockers can be beneficial. For example, in 1 randomized, double-blind, placebo-controlled trial, treatment with a combination of a β blocker, a calcium antagonist, and a long-acting nitrate significantly reduced the number and duration of symptomatic and silent ischemic episodes (Figure 2) and nitroglycerin consumption, compared with drug regimens that did not include a β blocker.8

In addition, the ultrashort-acting β blocker esmolol has now been shown to be very useful in patients with acute myocardial ischemia and moderate left ventricular (LV) dysfunction undergoing treatment in the coronary care unit. Patients treated with esmolol have demonstrated rapid reductions in arterial pressure, heart rate, and the rate-pressure product. Because esmolol has an elimination half-life of only about 9 minutes, the hemodynamic effects of the drug are rapidly lost following

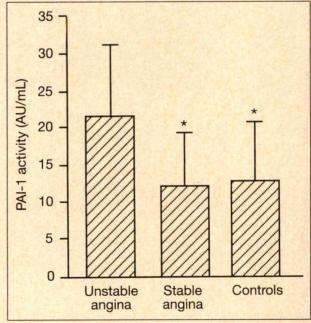


FIGURE 1. Plasminogen-activator inhibitor type 1 (PAI-1) levels in patients with stable and unstable angina. AU = arbitrary units. *p <0.02. (Adapted with permission from Circulation.4)

its discontinuation, making it particularly appropriate for use in patients with possible contraindications to B blocker therapy.

Calcium antagonists represent another medical approach to the management of unstable angina pectoris. These agents have been shown to decrease the number and duration of episodes of unstable angina and to reduce the need for bypass surgery. In 1 double-blind, placebo-controlled trial, fewer therapeutic failures, defined as sudden death, MI, or bypass surgery, occurred among patients who received nifedipine in addition to conventional therapy with a \beta blocker and nitrates than among those who received placebo along with conventional therapy. 10 This beneficial effect was especially marked in patients with ST-segment elevation during angina.

As previously mentioned, platelet aggregation is among the mechanisms responsible for the dynamic coronary obstruction that contributes to the pathogenesis of unstable angina. For this reason, thrombolytic therapy has been suggested as a possible treatment for this disorder. The small studies conducted to date to evaluate the efficacy of thrombolytic therapy in the management of unstable angina pectoris suggest that thrombolysis may be of benefit in patients with a coronary thrombus. Gold et al,11 for example, reported that unstable angina persisted in 6 of 11 patients who received conventional therapy and placebo but in only 1 of 12 patients treated with a 12-hour infusion of 1.75 mg/kg of recombinant human tissue-type plasminogen activator in addition to conventional therapy.

The third Thrombolysis in Myocardial Ischemia

(TIMI III) trial, now under way at many hospitals in the United States and Canada, should provide additional information regarding the value of thrombolytic therapy in the management of unstable angina. Specific issues being addressed in TIMI III include the effect of thrombolytic therapy on coronary flow and stenosis in unstable angina, which is being assessed by coronary angiography at 18 and 48 hours post-treatment, and the impact of cardiac catheterization and revascularization on outcome in patients with unstable angina.

The benefits of long-term aspirin therapy in patients with unstable angina were demonstrated in a 12-week Veterans Administration cooperative study by Lewis et al. 12 Death or MI occurred in 31 of the 625 study participants who were assigned to aspirin therapy and in 65 of the 641 who received placebo. This difference was statistically significant and represented a 51% reduction in the cardiac event rate in the aspirin treatment group. Similar findings were reported in a Canadian multicenter trial in which patients were followed for up to 2 years. 13 Again, the rate of cardiac death or nonfatal MI in the aspirin group (8.6%) was half that in the placebo group (17%).

EVALUATING THE EFFICACY OF MEDICAL REGIMENS FOR UNSTABLE ANGINA PECTORIS

Relief of disabling symptoms, prevention of MI and death, and control of ischemic activity are among the indicators that have been suggested for evaluating the efficacy of medical therapy among patients with unstable angina pectoris. Although subjective symptomatic relief is important, control of symptoms alone is an insufficient indicator of

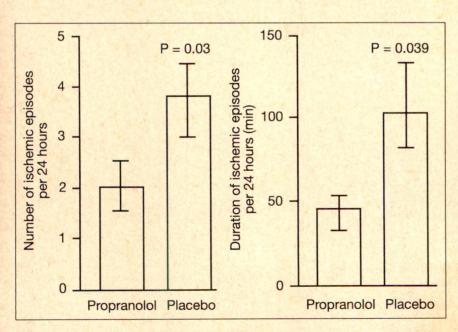


FIGURE 2. Number and duration of ischemic episodes (by continous electrocardiographic recording) in patients with unstable angina treated with a β blocker in combination with a nitrate and a calcium antagonist (propranolol) compared with ischemic activity in patients treated with a nitrate and a calcium antagonist plus placebo (placebo). (Adapted with permission from Circulation.7)

anti-ischemic activity. The assessment of the response of patients with unstable angina to medical therapy should center on objective techniques for measuring the severity of ischemic activity in an individual patient.

Exercise testing is one of these objective methods for evaluating the anti-ischemic effect of medical therapy in patients with apparent symptomatic relief. Evidence reported by Brown¹⁴ indicates that exercise testing plus thallium-201 perfusion imaging is highly predictive of outcome in patients with unstable angina whose symptoms resolve with pharmacologic treatment. During a mean follow-up of 39 ± 11 months, cardiac death or nonfatal MI occurred in 6 (26%) of 23 patients with thallium-201 perfusion defects that showed redistribution, representing jeopardized viable myocardium, compared with no deaths and only 1 MI among 29 patients with either a fixed perfusion defect or no perfusion abnormalities. Overall cardiac events, which included hospitalization for recurrent angina or revascularization as well as cardiac death and nonfatal MI, occurred in 16 (70%) of the patients with thallium-201 redistribution compared with 4 (29%) of the 14 with a fixed defect and 3 (20%) of the 15 with normal findings. The risk of cardiac events in patients with evidence of thallium-201 redistribution increased as the number of myocardial segments showing redistribution increased. The author concluded that the presence of thallium-201 redistribution in these patients was associated with a high risk of cardiac events, whereas its absence was linked with a low risk.

Ambulatory monitoring has also been used to assess the degree of ischemic activity in medically treated patients with unstable angina. Continuous ECG monitoring in a series of 70 patients with unstable angina whose symptoms were controlled with aggressive medical therapy in the intensive care unit indicated continued episodes of ischemia despite the absence of symptoms in 37.15 During the month following ambulatory monitoring, 6 of these patients developed MI, and 10 required bypass surgery or angioplasty for recurrent symptomatic angina. Of the 33 patients with no evidence of silent ischemia on ambulatory monitoring, only 1 went on to develop an MI and 3 required surgical intervention for recurrent angina.

OUTCOME OF CARDIAC CATHETERIZATION AND REVASCULARIZATION

Cardiac revascularization can be expected to control ischemia in the vast majority of patients with unstable angina. Such intervention also ap-

pears to improve survival in high-risk patients. There is some evidence that revascularization may improve LV function as well.

The advisability of routinely offering revascularization to all patients with unstable angina and suitable coronary anatomy awaits the results of TIMI IIIB. At present, however, there is general agreement that revascularization should be offered to all patients with unstable angina who fail to respond to medical therapy, that is, those who continue to experience symptoms or who demonstrate objective evidence of ongoing disease activity on treadmill testing or ambulatory monitoring. Success rates of >90% have been reported with emergency coronary angioplasty in patients who continued to have unstable angina despite intensive medical therapy.16

A randomized Veterans Administration Cooperative Study conducted by Luchi et al17 provided evidence of improved survival with revascularization plus medical therapy in a high-risk subset of patients with unstable angina. There was no difference in survival between patients treated with medical therapy alone and those who also underwent coronary artery bypass surgery for the study cohort as a whole. Revascularization did, however, prolong survival among patients with LV dysfunction, indicated by a reduced LV ejection fraction and triple-vessel disease, the same type of patient with improved survival in the Coronary Artery Surgery Study (CASS). 18 Mortality in patients with an LV ejection fraction of 30% was approximately 30% in the group that received medical therapy alone but only about 5% in those who also underwent surgery (Figure 3).

Evidence obtained in a study by Carlson et al¹⁹ suggests that revascularization may also improve LV function in patients with unstable angina. In this investigation, global and regional ejection fraction in jeopardized and, to a lesser extent, nonjeopardized myocardial segments increased significantly following coronary angioplasty in the 22 patients with unstable angina. No significant change in either global or regional LV function was observed in the 17 patients with stable angina who underwent angioplasty.

Several methods appear to be of value in determining which patients with unstable angina are most likely to experience improvement in LV function after revascularization. ECG changes constitute 1 of these measures. Persistent T-wave inversion has been shown to predict the reversal of segmental hypokinesis with angioplastic revascular-

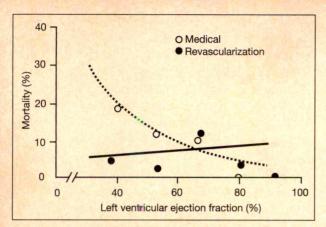


FIGURE 3. Association of left ventricular ejection fraction and mortality in patients with unstable angina treated with medical therapy alone and those treated with a combination of medical therapy and revascularization. (Adapted with permission from N Engl J Med. 16)

ization in patients with unstable angina and stenosis of the left anterior descending artery.²⁰

Reinjection of thallium-201 after initial thallium exercise scintigraphy and redistribution imaging may be another method of predicting the likelihood of improvement in LV function after revascularization. Dilsizian et al²¹ detected 85 apparently irreversible perfusion defects in 92 patients with unstable angina on thallium redistribution imaging at 3-4 hours after exercise scintigraphy. After a second injection of thallium, however, improvement was seen in 42 of these 85 segments. Thallium scintigraphy was repeated in 20 patients 3-6 months after coronary angioplasty. At this reevaluation, improvement indicated by normal thallium uptake and increased regional wall motion was apparent in 13 of 15 segments that had been identified as viable after reinjection of thallium in the study conducted before revascularization. In the 8 regions with persistent perfusion defects on thallium reinjection imaging before angioplasty, both thallium uptake and regional wall motion remained abnormal after angioplasty.

Because LV function is known to be the most important determinant of survival as well as of lifestyle and work status in patients with coronary disease, the determination of additional methods of predicting improvement in LV function with revascularization is being actively pursued. One of the newer techniques being evaluated for this purpose is the assessment of cardiac metabolism by nuclear magnetic resonance spectroscopy.

Finally, it is important to note that risk factor reduction may have a significant impact on the progression of the underlying atherosclerotic process in patients with coronary artery disease and that a careful assessment of such risk factors and appropriate intervention should be part of any therapeutic strategy.

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DISCUSSION

Participant: Is angioplasty or bypass surgery not routinely performed today in patients with anatomic lesions amenable to such intervention even before long-term medical management is attempted?

Dr. Gary Gerstenblith: That is often the case. Routine revascularization is offered to many patients with suitable anatomy. Whether or not routine revascularization is beneficial in these patients is being examined by the TIMI III study. The results of this important trial may alter our approach to the treatment of unstable angina.

Dr. Richard Gorlin: Although about half the patients with unstable angina have angiographic evidence of thrombosis, thrombolytic therapy is not very effective in this disorder. Of the 13 studies that have been performed, only between 3 and 5 have detected clinical or angiographic evidence of efficacy. Can you speculate as to why thrombolytic therapy is so ineffective in unstable angina?

Dr. Gerstenblith: A difference in the efficacy of thrombolytic therapy may be related to differences in the composition of thrombi in patients with unstable angina and acute infarction. In a recent study by Mizuno and colleagues1 using coronary angioscopy, patients with unstable angina had predominantly grayish-white, nonocclusive thrombi, whereas those with acute infarction had reddish thrombi, which were occlusive.

Participant: Could part of the reason also be that most cases of unstable angina do not involve complete thrombotic occlusion? Therefore, you are not attempting to salvage the myocardium as in patients with acute myocardial infarction.

Dr. Gerstenblith: Yes, that may be true. There may be additional pathophysiologic components.

Dr. Udho Thadani: I find it very difficult to justify the use of thrombolytic therapy in unstable angina when 10% of patients have normal coronary arteries and the use of tissue-type plasminogen activator is associated with about a 0.6% incidence of stroke, which is probably more devastating than myocardial infarction. With 10 negative studies, I think it is very difficult to accept the role of thrombolytic therapy in unstable angina when the mortality and infarct rate in these patients during routine use of aspirin and intravenously administered heparin are so low. What are your comments

Dr. Gerstenblith: Our practice now is to use thrombolytic therapy in those patients in whom we have demonstrated a significant thrombus at cardiac catheterization.

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Pharmacologic Mechanisms of Nitrates in Myocardial Ischemia

Jay N. Cohn, MD

Nitrates exert both hemodynamic and nonhemodynamic effects that help explain the mechanisms by which these drugs benefit patients with myocardial ischemia. The hemodynamic effects of nitrates include relaxation of conduit arteries. increased arterial compliance, increased venous capacitance, dilation of collateral vessels in the myocardium, and, possibly, increased myocardial compliance. A growing body of evidence suggests that the nonhemodynamic effects of these agents include inhibition of vascular smooth muscle growth and of myocyte hypertrophy and ventricular remodeling. Since endothelial function appears to be abnormal in patients with myocardial ischemia and nitrates replicate many of the effects of endothelium-derived relaxing factor, these drugs may be viewed as a pharmacologic replacement for deficient endogenous activity. (Am J Cardiol 1992;70:38G-42G)

growing understanding of the vascular and tissue effects of nitrates suggests that these agents can be expected to provide benefit in a broad range of coronary artery disease (CAD) syndromes. In addition to their efficacy in the management of exertional angina, unstable angina, and silent ischemia, nitrates may prove useful in patients with acute myocardial infarction, left ventricular (LV) diastolic dysfunction, and congestive heart failure (CHF) with elevated central venous pressure. In combination with hydralazine, nitrates may also play a role in the management of LV systolic dysfunction and reduced exercise capacity.

The anti-ischemic effects of nitrates are related to improvements in both myocardial oxygen supply and demand. On the supply side, they improve blood delivery by reducing stenosis resistance, improving collateral flow, and improving subendocardial perfusion through reduction of the compressive forces on the subendocardium during diastole. Nitrates also decrease myocardial oxygen demand by lowering systolic blood pressure and modestly reducing end-diastolic ventricular volume. The pharmacologic actions of nitrates are so diverse that the mechanism by which they relieve myocardial ischemia most likely varies according to the coronary anatomy and LV function of the individual patient.

Nitrates may potentially exert favorable effects at several points in the cycle of CAD and LV dysfunction (Figure 1): (1) Nitrates can prevent the ischemic manifestations of CAD, perhaps largely by dilating the coronary arteries or improving collateral perfusion. (2) When CAD manifestations—myocardial infarction or simply ischemia do occur, nitrates may prevent LV systolic dysfunction by either relieving ischemia or improving systolic performance. (3) In the presence of LV systolic dysfunction, nitrates may play a role in preventing the progression to hypertrophy and dilation, as well as subsequent increases in myocardial oxygen consumption that can further aggravate ischemia. (4) Nitrates may also favorably affect subendocardial ischemia by preventing or

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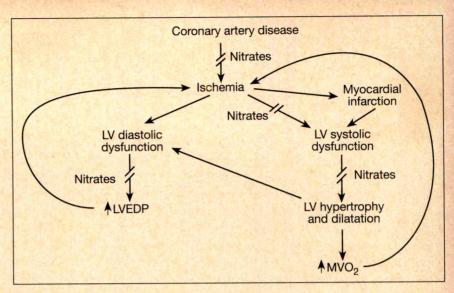


FIGURE 1. Vicious cycles of coronary artery disease and left ventricular (LV) dysfunction.

ameliorating the increase in LV end-diastolic pressure, particularly during exercise.

HEMODYNAMIC MECHANISMS

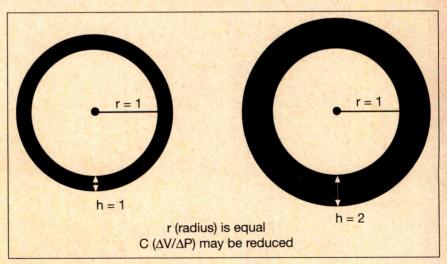
Therapeutic responses to nitrates result from both hemodynamic and nonhemodynamic effects. Important factors in the hemodynamic actions of these drugs include dilation of conductance arteries in the coronary system, as well as in the pulmonary bed and systemic circulation; an increase in arterial compliance; and an increase in venous capacitance. In some clinical situations, increased coronary collateral flow may also be important. Only mild arteriolar dilation occurs, which has little effect on systemic vascular resistance. The suggestion that nitrates may also increase myocardial compliance remains controversial; it is difficult to separate pressure effects from direct compliance effects.

Resistance versus compliance: Effects on vascular resistance and vascular compliance reflect the actions of very different hemodynamic mechanisms. The compliance of a blood vessel can be profoundly affected without any change in caliber, which is the major determinant of its resistance to blood flow. Two arterioles of equal radius will have the same resistance; however, if the second arteriole has a thickened wall, it will have greater resistance to stretch or volume change with pulsation than the first (Figure 2). Thus, compliance $(\Delta \text{ volume}/\Delta \text{ pressure})$ will be reduced in the arteriole with the thicker wall, but the resistance may be the same in both arterioles.

In the case of a large artery proximal to the resistant site, compliance constitutes the major contribution of the artery to circulatory homeostasis, because there is not a significant pressure drop along the conduit arteries. Therefore, a change in conduit artery tone will not alter resistance but may profoundly affect the compliance of the artery, the storage capacity during systole, or the generation of oscillatory waves in the smaller arteries downstream.

The importance of this control system in the

FIGURE 2. Vascular resistance versus vascular compliance (C). P = pressure; V = volume; h = thickness of arterial wall.



circulation is becoming increasingly evident and may help explain some of the therapeutic effects of nitrates. Although nitrates may not alter wall thickness acutely, they certainly influence the compliance of a vessel and allow a greater change in pulsatile caliber. This change may result in a striking alteration in the storage capacity of the large arteries and in the generation of reflected waves—a consideration that is often not even addressed during patient assessments.

In experiments conducted in our laboratory, we have measured compliance using diastolic pulse wave analysis following infusion of nitrodilators. The data revealed a dramatic increase in the compliance characteristics that generate reflected waves, with no change in calculated resistance. Therefore, even though mean blood pressure and cardiac output may not change, the drug is nonetheless exerting a major pharmacologic effect on the vasculature.

Exercise response: Nitrates that are used to block ischemia during exercise can prevent an increase in end-diastolic pressure and produce a profound increase in exercise capacity. However, even in the absence of ischemia in individuals with CAD, nitrates affect the hemodynamic response to exercise.

We conducted a study in which 18 patients with CHF performed bicycle exercise before (control) and 90 minutes after receiving a 40 mg oral dose of isosorbide dinitrate.1 Mean heart rates at rest and during submaximal and maximal exercise were comparable before and after administration of the drug. Although mean blood pressure at rest was lower after patients received isosorbide dinitrate than before, it increased to a similar degree during exercise both with and without the drug. Isosorbide dinitrate had no profound effect on cardiac output. In contrast, mean pulmonary wedge pressure at rest was strikingly lower after administration of the drug; it remained lower during submaximal exercise, but this benefit was lost during peak exercise. Similarly, isosorbide dinitrate tended to reduce mean systemic vascular resistance at rest and at submaximal workloads, but not at maximal exercise.

The results of this study suggest that even patients without ischemia, such as those with CHF, might be able to perform submaximal exercise more comfortably and for longer periods with nitrate therapy. These observations also suggest that clinicians should evaluate the effect of nitrates at submaximal exercise, where their hemodynamic effects are most prominent. If only peak exercise

data are obtained, the beneficial effect of the nitrate may not be identified.

Response to chronic therapy: Despite the well-known phenomenon of nitrate tolerance in some patients, we showed in our randomized, placebo-controlled study that the hemodynamic benefits of isosorbide dinitrate are sustained during chronic therapy in CHF patients.² Among those who received isosorbide dinitrate, 40 mg 4 times daily, pulmonary wedge pressure was significantly lower after 3 months of therapy compared with prerandomization control values (-2.5 ± 0.9 mm Hg). No significant change occurred in the placebo group. At 3 months, patients in the isosorbide dinitrate group received a single 40 mg dose of the drug and responded with a further 5.4 ± 1.5 mm Hg decrease in wedge pressure, unlike those in the placebo group, whose wedge pressure did not change significantly after a single dose of placebo.

Three months of nitrate therapy, which might have been expected to induce some degree of tolerance, had thus produced a change in the baseline hemodynamics of these patients. Further, the effect of the drug appeared to persist, as shown by the continued response of the treated patients, despite chronic therapy.

Effects on left ventricular dysfunction: The favorable effects of nitrates on LV dysfunction are related to both hemodynamic and nonhemodynamic factors (addressed below). A decrease in LV end-diastolic volume results from increased venous capacitance and stroke volume. The response to the decrease in ventricular end-diastolic volume includes decreased wall stress, lower pulmonary capillary pressure, reduced mitral valve regurgitation, and improved subendocardial perfusion and metabolism.

Nitrates also reduce aortic impedance as the result of increased large-artery compliance, decreased reflected waves in systole, and arteriolar dilation. The decrease in aortic impedance results in decreased wall stress and myocardial oxygen consumption, increased stroke volume, and lower end-diastolic volume.

NONHEMODYNAMIC MECHANISMS

An emerging body of evidence points toward nonhemodynamic mechanisms of action whereby nitrates inhibit vascular smooth muscle growth as well as myocyte hypertrophy and ventricular remodeling.

Nonhemodynamic factors contributing to the favorable effects of nitrates on LV dysfunction include inhibition of vascular growth and hypertrophy as well as slowed progression of ventricular dilation, resulting in reduced impedance. Impedance is related to the compliance of the aorta and arteries, both of which are affected by nitrates. Impedance is also related to arteriolar resistance, which is only modestly affected by nitrates. When impedance is lowered in patients with CHF, stroke volume increases.

In patients with CHF and ischemic heart disease, the combination of nitrates and hydralazine has a favorable effect on survival, as shown in the first and second Veterans Administration Cooperative Vasodilator-Heart Failure Trials (VHeFT).3,4 Chronic therapy with this combination also improves LV systolic function. In VHeFT I, the ejection fraction progressively worsened over 4.5 years in the placebo group, whereas systolic function was maintained in the group receiving hydralazine and nitrates.³ In VHeFT II, 2-year follow-up data showed that patients receiving this combination exhibited greater improvement in systolic function and in peak exercise oxygen consumption than patients treated with enalapril.4

Animal studies conducted in our laboratory have provided insights into the nonhemodynamic mechanisms by which nitrates may influence progression of LV dysfunction.⁵ These experiments involved the use of a dog model in which a direct current shock to the left ventricle caused scarring and thinning in the apical area, and dilation and hypertrophy of the rest of the ventricle. After 1 week LV mass began to increase, as confirmed with magnetic resonance imaging, and by 16 weeks the left ventricle was dilated and hypertrophied. However, when an angiotensin-converting enzyme (ACE) inhibitor was given the day after administration of the electric shock, there was no increase in LV mass and attenuation of the increase in LV volume. At 16 weeks the ventricle was considerably less dilated in the treated hearts than in the controls, indicating that the ACE inhibitor had blocked the process of hypertrophy and remodeling.

Using the same dog model, we studied the effects of isosorbide mononitrate, 30 mg twice daily, on LV dysfunction.⁶ After 1 week the isosorbide mononitrate-treated hearts exhibited no increase in either LV mass or LV volume. After 16 weeks both mass and volume had increased in the placebo group but remained unchanged in the nitrate-treated group.

These effects of isosorbide mononitrate do not appear to be hemodynamic in nature, because the measurable hemodynamic effects of the drug per-

TABLE | Nitrates Versus Endothelium-Derived Relaxing Factor (FDRF)

	Nitrates	EDRF
1	Stimulate cyclic-GMP	Stimulates cyclic-GMP
	Exogenously administered	Endogenously released
	Prolonged circulatory effect	Transient circulatory effect
	Increased activity in CAD (?)	Decreased release in CAD
	Systemically effective	Locally effective
	Inhibit VSM growth	Inhibits VSM growth
	Inhibit myocyte growth	Inhibits myocyte growth
	Tolerance to hemodynamic effect	No tolerance demonstrated
	CAD = coronary artery disease; GMP =	guanosine monophosphate; VSM =

sist for only about 2 hours following acute administration in the dog model. The effects on LV mass and volume, on the other hand, persist chronically in the absence of any measurable hemodynamic effects. The mechanism of benefit may be related to stimulation of guanosine monophosphate at the tissue level⁷ and may be independent of a demonstrable vascular effect of the nitrate.

Nitrates might be viewed as a potential pharmacologic replacement for deficient endothelial function in patients with ischemic heart disease. Such individuals appear to have abnormal endothelial function, and the nitrates replicate many of the effects of endothelium-derived relaxing factor (see Table I).

CONCLUSION

In the natural development of LV dysfunction from ischemic heart disease, both myocardial and peripheral progression play key roles. Symptoms are most likely related to the peripheral factors, including vasoconstriction and impedance, whereas progression and mortality are related to changes in the left ventricle. The nitrates appear to act on both ends of the spectrum by preventing remodeling as well as reducing impedance and vasoconstriction in the periphery.

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DISCUSSION

Dr. Uri Elkayam: How is compliance measured? What is the clinical relevance of such measurements when none of the other hemodynamic parameters change?

Dr. Jay N. Cohn: One technique looks at the late systolic peak in the arterial pulse wave. Reflected waves arriving at the root of the aorta in systole will add a load to the left ventricle that cannot be assessed by sphygmomanometry or even by recording peripheral arterial pressure. When a nitrate is administered, the late systolic peak disappears; therefore, even though the mean pressure does not change, left ventricular load is reduced. In addition, when a nitrate is administered, the systolic pressure may decrease, the diastolic pressure may actually increase, and the mean pressure may remain unchanged, but left ventricular systolic work is reduced because stroke volume is being emptied against a lower mean systolic pressure. The diastolic pressure remains elevated because the aorta has been loaded during systole and now releases a larger amount of its volume in diastole to support diastolic pressure.

I believe that when we simply measure mean pressure and cardiac output to assess the vasculature, we are missing an important component of the pulsatile nature of flow and pressure.

Tolerance, Rebound, and Time-Zero Effect of Nitrate Therapy

William H. Frishman, MD

Both nitroglycerin and long-acting nitrates have proved effective in treating acute anginal pain. In recent years, however, development of tolerance with the continuous use of these agents has been documented. A pilot study demonstrated attenuation of the therapeutic effect of high-dose, continuous transdermal nitroglycerin therapy, despite adequate plasma nitroglycerin levels. In a subsequent, larger Transdermal Nitroglycerin Cooperative Study, evidence of tolerance was detected within 24 hours of initiation of continuous nitroglycerin patch therapy at several different dose levels. Sustained pharmacologic activity has been achieved with the intermittent use of transdermal nitroglycerin, usually for 12 hours followed by a 12-hour drug-free period. When the patch is discontinued, however, some patients experience exacerbation, or rebound, of anginal symptoms and a worsening of exercise tolerance at the end of the drug-free period. Additional clinical research is therefore needed to determine the optimal intermittent dosing strategy.

(Am J Cardiol 1992;70:43G-48G)

itrates have been used as an effective treatment for angina pectoris for > 100 years. Their antianginal activity is attributable to a number of mechanisms, which include peripheral arterial and venous dilation, the dilation of coronary arteries, the opening of intercoronary collateral vessels, and the prevention of coronary artery vasospasm.1 Sublingual nitroglycerin was the earliest form of nitrate therapy, followed by longer-acting oral nitrates, such as isosorbide dinitrate, which were introduced in the late 1930s. In recent years a variety of newer nitrate-delivery systems, including oral sprays, buccal/transmucosal preparations, ointments, and transdermal disks and patches, have been developed, and researchers continue to seek innovative approaches to nitrate delivery.1,2

Reports of the development of tolerance to the effects of nitrates and descriptions of the loss of antianginal activity can be found in the early scientific literature.2 More recently, a study by Parker et al³ in 12 patients with chronic stable angina pectoris demonstrated an attenuation of the effect of oral isosorbide dinitrate on treadmill walking time with increased frequency of administration. The increase in exercise time to the onset of moderate angina noted 3 and 5 hours after the nitrate dose in patients treated with a 4 times daily regimen was diminished compared with exercise capacity in patients treated 2 or 3 times daily. In fact, at the 5-hour evaluation, exercise duration in patients treated with the 4 times daily regimen was actually lower than the baseline value.

EVALUATION OF CONTINUOUS TRANSDERMAL NITROGLYCERIN THERAPY

Transcutaneous nitroglycerin patches were initially approved for use in the United States on the basis of data demonstrating that equivalent blood nitroglycerin concentrations were obtained with sublingual and patch formulations. Very little patient efficacy information was available until after these transcutaneous preparations were approved for clinical use. As experience with transdermal

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nitroglycerin widened, reports of the development of tolerance with continuous patch therapy began to appear.

The development of tolerance with continuous transcutaneous delivery of very-high-dose nitroglycerin therapy was examined in a pilot study conducted in 20 patients.4 Responsiveness to sublingual nitroglycerin was required for study admission. The nitroglycerin dose was titrated up to 10 patches (100 mg daily) during an initial 48-hour titration phase. Baseline angina activity was re-established during a subsequent washout period, after which patients were randomly assigned to treatment with patches containing either placebo or nitroglycerin. These patients were then followed for a 2-week double-blind treatment period. During this time, serial exercise stress tests were conducted both before and 4 and 24 hours after application of the patch.

At the end of 2 weeks, blood nitroglycerin levels in patients treated with the transdermal patches were clearly higher than those achieved with sublingual nitroglycerin administration. The mean nitroglycerin concentration after sublingual therapy was 0.32 ng/mL compared with 4.04 ng/mL after 2 weeks of treatment with the transdermal patch. These findings provided evidence that nitroglycerin was being delivered systemically and that any development of tolerance could not be attributed to malabsorption of the drug through the skin.

Systolic blood pressure monitoring during the 2-week double-blind treatment period indicated an attenuation of the blood pressure-lowering effect of nitroglycerin over time. Four hours after application of the first patch, preexercise systolic blood pressure of patients treated with the active medication was significantly lower than that of placebotreated patients. At 24 hours the systolic blood pressure level remained significantly lower in the nitroglycerin-treated group than in the placebo group. After 1 and 2 weeks of treatment, however, the effect of nitroglycerin on blood pressure was diminished, and the differences between the 2 treatment groups were no longer statistically significant. Heart rate showed a similar pattern of response. Initially, transdermal nitroglycerin delivery resulted in about a 10% increase in heart rate, but this effect dissipated with continued administration.

The dissipation of the hemodynamic effects of transdermal nitroglycerin was accompanied by an attenuation of its antianginal effect. Although patients treated with nitroglycerin initially demonstrated improvement in exercise tolerance, this effect declined with time. Intracellular sulfhydryl depletion, neurohormonal activation, and intravascular volume expansion are among the mechanisms suggested for the development of tolerance with continuous exposure to nitroglycerin.

The findings of this pilot study led the U.S. Food and Drug Administration (FDA) to request a larger follow-up study with an initial enrollment of 751 patients to establish proof of efficacy and lack of tolerance with the continuous use of transdermal nitroglycerin preparations.⁵ This cooperative study, supported by the manufacturers of the 3 nitroglycerin patches, compared the effect on treadmill exercise time of the continuous administration of low (15 and 30 mg/day), medium (45 and 60 mg/day), and high (75, 90, and 105 mg/day) doses of transdermal nitroglycerin with that of placebo in 562 patients randomized to double-blind therapy. In addition, the extent to which tolerance developed during continuously applied therapy was assessed, patients were evaluated for a doseresponse effect, and the need for high doses in order to achieve a long-term response was examined.

The study began with a baseline period of 1-4 weeks, which was followed by a dose-titration phase of up to 6 weeks. Patients were treated with a fixed-dose transdermal nitroglycerin regimen for the next 2 weeks. The study concluded with a 2-week detitration period.

Exercise testing was conducted according to the Bruce protocol. As in the earlier pilot study, testing was performed just before and 4 and 24 hours after patch application. In addition to exercise testing, the frequency of anginal attacks, sublingual nitroglycerin consumption, and blood pressure and heart rate prior to exercise testing were determined.

On the first day of treatment, exercise testing 4 hours after patch application showed a significant increase in treadmill walking time with the 3 nitroglycerin preparations. A mean increase from baseline of approximately 50 seconds was observed in all 3 active treatment groups as compared with about a 15-second increase in the placebo group (Figure 1). By 24 hours, however, the effect of nitroglycerin was no longer apparent, and no significant differences were noted between patients in the nitroglycerin treatment groups and the group assigned to receive placebo. Exercise testing repeated after 14 days and again after 8 weeks of transdermal nitroglycerin therapy likewise indicated no differences between the 337 nitroglycerintreated and the 118 placebo-treated patients who completed the testing.

The reason for the lack of significant differences in exercise capacity between the nitroglycerin and placebo treatment groups may be due in part to a training effect resulting from repeated stress testing. Most investigators consider a 20% improvement in exercise time from baseline an indication of a clinical effect. In this study, such improvement was achieved with placebo. In fact, progressive improvement was seen in the placebo-treated patients with each stress test. The opening of collateral coronary vessels in response to exercise is another possible explanation for the increase in exercise performance noted in the placebo group.

A post hoc analysis of the study data suggested that transdermal nitroglycerin therapy may have affected the frequency of angina attacks in patients with a higher frequency of such episodes. Although these patients demonstrated no significant improvement in exercise tolerance compared with the placebo group, they did experience fewer spontaneous attacks of angina during the day.

In summary, the transdermal nitroglycerin cooperative study provided evidence of the attenuation of the effects of nitroglycerin within the first 24 hours of continuous therapy. This lowering of responsiveness persisted throughout the 8-week study. Although exercise capacity in the nitroglycerin-treated patients did show an increase over baseline, a similar degree of improvement was seen in patients treated with placebo. Because of these

findings, the FDA now recommends that transdermal nitroglycerin patches not be used on a continuous basis.

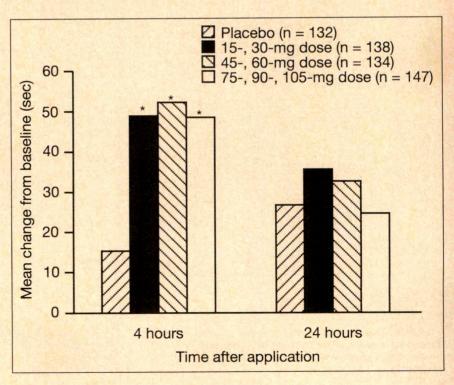
EVALUATION OF INTERMITTENT NITROGLYCERIN THERAPY

Results of the first large study to assess the efficacy of intermittent transdermal nitroglycerin dosage strategies in patients with chronic stable angina were reported in 1989.⁶ Criteria for inclusion in this double-blind, randomized, placebocontrolled, multicenter trial included a primary diagnosis of angina pectoris, the development of moderate angina within 3–7 minutes, objective evidence of coronary artery disease, responsiveness to nitrates as confirmed by exercise testing, and reproducible exercise test results. The 206 patients accepted into the study were not permitted to use any other antianginal drugs, with the exception of β blockers and sublingual nitroglycerin.

Patches designed to deliver placebo or 5–20 mg/day of nitroglycerin were applied for a period of 12 hours each day for 4 weeks. The 12-hour treatment period was followed by a 12-hour patchfree interval. The response to nitroglycerin was evaluated by exercise testing conducted before patch application and 4, 8, and 12 hours after application on days 1, 15, and 29.

Exercise tests performed on day 1 of the study indicated persistence of the antianginal effect of transdermal nitroglycerin throughout the 12-hour

FIGURE 1. Mean change from baseline in treadmill walking time on day 1 with placebo and with continuous transdermal nitroglycerin therapy in the Transdermal Nitroglycerin Cooperative Study. *p = 0.05 vs placebo. (Adapted with permission from Am J Cardiol.5)



application period. This beneficial effect was seen with both the lower-dose (5–10 mg/day) and higherdose (15-20 mg/day) patches. The exercise time to moderate angina was significantly greater in patients treated with the higher nitroglycerin doses than in the placebo group at 4, 8, and 12 hours. Exercise time in patients treated with the lower doses of the drug was also greater than in the placebo group at each evaluation period, but only the difference at 12 hours was statistically significant.

Some persistence of this effect was apparent on day 15, when exercise time to moderate angina was significantly greater with the higher-dose nitroglycerin patches than with placebo at 4 and 8 hours. This finding contrasted with the loss of effect noted in the continuous treatment trial.

On day 29, an effect of the higher-dose nitroglycerin patches on exercise time was seen at the

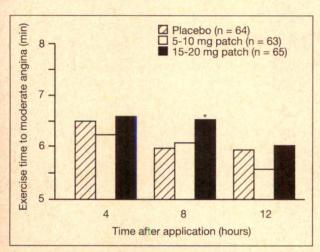


FIGURE 2. Exercise time to moderate angina on Day 29 with placebo and intermittent transdermal nitroglycerin therapy. *p = 0.05 vs placebo. (Adapted with permission from J Am Coll Cardiol.6)

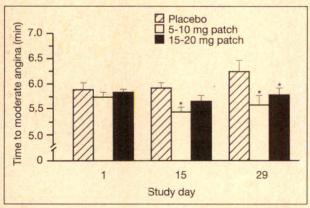


FIGURE 3. Zero-hour response associated with prolonged intermittent transdermal nitroglycerin therapy. *p = 0.05 vs placebo. (Adapted with permission from J Am Coll Cardiol.6)

8-hour evaluation (Figure 2). At 12 hours, however, there was an attenuation of the response to nitroglycerin, similar to but perhaps not as great as that seen with continuous therapy. Thus, no striking differences between nitroglycerin-treated and placebo-treated patients were apparent on day 29 at 4 and 12 hours. Nevertheless, these findings led the FDA to recommend an intermittent dosing strategy for the nitroglycerin patches rather than a continuous dosing regimen.

ZERO-HOUR RESPONSE

One of the concerns with intermittent transdermal nitroglycerin therapy is the zero-hour response, or time-zero effect. The zero-hour response is manifested by poorer performance than placebo-treated patients on a predose exercise stress test at the end of the drug-free interval.

Evidence of the zero-hour response was seen in the multicenter intermittent transdermal nitroglycerin trial. As shown in Figure 3, exercise time to moderate angina at the end of the 12-hour nitroglycerin-free period on day 15 and day 29 indicated greater improvement in placebo-treated patients than in those treated with the nitroglycerin patches. In addition to the apparent loss of the effect on exercise performance with prolonged nitroglycerin therapy, the potential also exists for a worsening of angina with patch withdrawal, particularly when long dosing intervals are employed. Some patients may even experience worsening of angina during

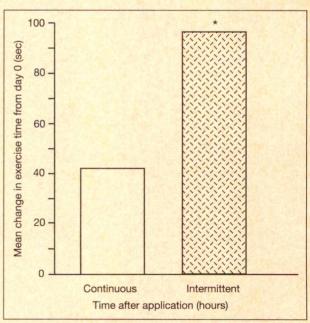


FIGURE 4. Comparison of the mean change from baseline in exercise time after 14 days of treatment with continuous or intermittent transdermal nitroglycerin. *p = 0.001 vs placebo. (Data from Am J Cardiol.7)

the nitroglycerin-free period. In fact, in the multicenter trial of intermittent therapy, 9 of 138 nitroglycerin-treated patients but none of those treated with placebo experienced a significant increase in rest angina during the nitroglycerin-free period. However, all 9 patients remained in the study, and their angina was self-limited or managed with sublingual nitroglycerin. This increase in rest angina was not related to the transdermal nitroglycerin dose.

PERSISTENT VERSUS INTERMITTENT THERAPY

A clinical trial conducted in the Netherlands compared the response to continuous versus intermittent treatment with transdermal nitroglycerin.7 This randomized, double-blind, placebo-controlled study involved 108 patients with severe angina. These patients were assigned to treatment with placebo or with either continuous or intermittent transdermal nitroglycerin therapy. The nitroglycerin dose of 0.4 mg/hour was provided by a 20 cm² patch. Patients in the continuous therapy group wore the patch for a full 24 hours each day. Intermittent therapy consisted of a 14-hour treatment period, followed by a 10-hour nitroglycerinfree period. The duration of treatment was 14 days. Bicycle ergometry performed at 2-10 hours after patch application was used to determine the response to treatment.

Exercise testing at the end of the 14-day treatment period indicated a greater effect with the intermittent than with the continuous regimen (Figure 4). Exercise time in patients assigned to intermittent therapy increased by >80 seconds and was significantly greater than in patients treated with placebo. The mean change in exercise time in the continuous treatment group was about 40 seconds. Improvement in this group did not differ significantly from that in placebo-treated patients.

CONCLUSION

Nitroglycerin is clearly an effective therapy for the management of angina. The evidence obtained in clinical trials of transcutaneous nitroglycerin patches in patients with angina, however, indicates an attenuation of both the hemodynamic effects of nitroglycerin and its effects on exercise capacity with continuous therapy. Intermittent dosing strategies appear to preserve the effect on exercise, although the safety of intermittent therapy and the optimal dosing regimens for maximizing its beneficial effects remain to be established.

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DISCUSSION

Participant: How would you interpret the data you presented in light of the frequent use today of prolonged intravenous nitroglycerin therapy for acute ischemic syndromes? Does the response of the acute syndromes differ when intravenous nitroglycerin is used?

Dr. William H. Frishman: Tolerance to intravenous nitroglycerin develops fairly rapidly. Frequently, the dose must be up-titrated in the coronary care unit. It is not known whether this is due to an attenuation of the effect of nitroglycerin or to a worsening of the condition being treated. I am convinced that many patients with stable angina do improve with intravenous nitroglycerin, but attenuation of the effect occurs rapidly. Consequently, the improvement seen in the coronary care unit may just represent stabilization, which is known to occur with time in patients with unstable angina.

Dr. Ezra A. Amsterdam: There is another possible explanation for the improvement in serial exercise test performance seen in these studies. One to 3 treadmill tests every few days is not sufficient to yield a classic physiologic training effect. It does, however, increase biomechanical efficiency. Patients who become accustomed to treadmill exercise are able to perform better because of a decrease in total body rate of oxygen consumption (VO₂) with the same external workload, thereby reducing heart rate and blood pressure response to exertion. That is, they can perform a certain level of exercise at a lower total body VO₂ because they know how to walk "better." This effect is inevitable, even in patients who have performed exercise treadmill tests in the past. They become more comfortable and less nervous and so the VO₂ per load on the treadmill decreases. It is not a classic physiologic training effect, but it affects performance. The only way we will be able to determine the significance of such an effect is to measure the actual VO₂ during stress testing.

Dr. Frishman: I agree. The other finding that has surprised us in recent years is that improvement with effective therapies is much more modest now than has been documented in the past, possibly because of increased exercise testing and its effect in placebo-treated patients. In addition, patients were previously evaluated at peak dosing rather than at the end of the dosing interval. Today, we are required to conduct studies at the end of the dosing interval, and we see a much more modest effect of treatment.

Dr. Amsterdam: Not all patients with chronic stable angina will respond to nitroglycerin. The very modest statistically significant data that you

showed may include many patients who are not responding to the nitroglycerin patches.

Dr. Frishman: In our pilot study, we found this attenuation of effect in 20 patients who had been shown to be responsive to sublingual nitroglycerin. It is a real effect and not just related to the fact that some nonresponders may be included. We considered 24 patients for admission to the study and excluded 4 because they did not respond to nitroglycerin.

Dr. Amsterdam: My point is that the small number of patients culled to participate in such studies constitute the best responders to nitroglycerin. In fact, these therapies are widely used in patients who will never respond and never demonstrate a statistically significant benefit.

Possible Mechanisms of Nitrate Tolerance

Uri Elkayam, MD, Anil Mehra, MD, Avraham Shotan, MD, Enrique Osprzega, MD

Prolonged exposure to organic nitrates has been shown to lead to the rapid development of tolerance to the peripheral and coronary vasodilatory effects of these drugs. As a result of this phenomenon, the hemodynamic and anti-ischemic effects of nitrates may be rapidly attenuated in patients with ischemic heart disease, congestive heart failure, or both. This nitrate tolerance appears to be both dose- and time-dependent. Likely mechanisms proposed for its development are multifactorial and include depletion of sulfhydryl groups, a nitrate-mediated increase in blood volume, and neurohormonal stimulation with activation of vasoconstrictive mechanisms.

(Am J Cardiol 1992;70:49G-54G)

he rapid development of tolerance with prolonged exposure to organic nitrates is well documented in the scientific literature. Nitroglycerin tolerance was described as early as 1905 by Steward, who expressed frustration at an inability to overcome tolerance to the drug, despite a 160-fold increase in the nitrate dose level. The development of immunity to the undesirable side effects of nitroglycerin, particularly headache, within 3-4 days by workers engaged in its manufacture further suggested nitrate tolerance.2 This immunity was lost rapidly, as indicated by the reappearance of symptoms of nitroglycerin toxicity after an absence from work of only a few days. For this reason, it became common practice for nitroglycerin workers to place some of the product in their hatbands during periods of absence from the factory so as to maintain their immunity. Thus as early as 1914 the importance of intermittent exposure to nitrates for the maintenance of the drug effect was being recognized.2

A recent review of data from 22 studies conducted between 1980 and 1989 provided strong evidence for the development of nitrate tolerance in patients with angina pectoris.3 These patients were treated with various types of nitrate preparations, including standard and sustained-release oral formulations, transdermal systems, and intravenous formulations, for periods ranging from 1 day to 2 months.

Despite considerable data supporting the occurrence of nitrate tolerance, its clinical importance has been questioned in the past. This earlier skepticism was attributable to findings such as those of Danahy and Aronow.4 These investigators conducted treadmill exercise tests in 21 men with typical effort angina 1, 3, and 5 hours after an initial oral dose of isosorbide dinitrate (ISDN) or placebo. Exercise performance at all 3 evaluation periods was enhanced in the ISDN-treated patients compared with placebo. When the researchers repeated exercise testing after a mean of 5.6 months of treatment with ISDN, they found that the antianginal effect of the drug was maintained. Careful examination of the protocol followed in this study, however, revealed that patients were

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allowed a 16-hour nitrate-free interval prior to the reevaluation of ISDN effect. Similarly, a period of nitrate withdrawal was also used by Franciosa and Cohn,5 who reported persistence of the hemodynamic effect of ISDN in patients with congestive heart failure. Nevertheless, the information available in the early 1980s led to the conclusion that prolonged therapy with long-acting nitrates was not associated with clinically important tolerance, even when these agents were used in large doses.6

MANIFESTATIONS OF NITRATE TOLERANCE

There are other data, however, to support the rapid and marked attenuation of all aspects of nitrate activity, including effects on the peripheral and coronary circulation and on platelet activity, with continuous exposure or frequent dosing.

Effect on peripheral circulation: A 1985 study by Manyari et al⁷ demonstrated a significant increase in regional blood volume, measured by the radionuclide blood pool method, in patients with stable angina after an initial dose of 0.6 mg of sublingual glyceryl trinitrate. After 4 weeks of treatment with ISDN, the response to glyceryl trinitrate was markedly attenuated (Figure 1). The earlier changes in blood pressure and heart rate achieved with glyceryl trinitrate were also signifi-

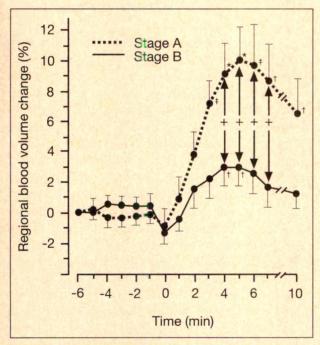


FIGURE 1. Changes in regional blood volume in response to sublingual nitroglycerin during a control period (stage A) and after 4 weeks of treatment with isosorbide dinitrate (ISDN; stage B). Patients received 0.6 mg of sublingual nitroglycerin at time 0. *p < 0.05; +p < 0.01; ‡p < 0.001 versus value before nitroglycerin; the plus sign between the vertical arrows indicates p < 0.05 for stage A versus stage B at the time given on the abscissa. (Adapted with permission from Am J Cardiol.7)

cantly diminished at this repeat evaluation. Thus the study not only showed attenuation of the peripheral effect of nitrates with long-term therapy but also established the existence of cross-tolerance between ISDN and sublingual nitroglycerin. Attenuation of the effect of nitroglycerin on pulmonary arterial wedge pressure (PAWP) in patients with congestive heart failure treated with continuous intravenous infusion of the drug has also been reported. In 1 study by our group, 8 patients whose PAWP fell by at least 30% or 10 mm Hg in response to intravenous nitroglycerin were randomly assigned to receive placebo or to continue on nitroglycerin therapy. An immediate increase in PAWP occurred in the placebo group. In contrast, PAWP in patients who continued to receive nitroglycerin was significantly lower than at baseline for the first 8 hours of the infusion period. After that time, however, PAWP in the nitroglycerin treatment group began to rise, and values recorded at 12, 20, and 24 hours were no different from those noted in the placebo group.

Attenuation of effect on coronary circulation: There is also evidence for the attenuation of the effect of nitrates on the coronary circulation. May et al9 demonstrated a reproducible, doserelated increase in coronary sinus blood flow in a group of 19 subjects (17 with coronary artery disease) after administration of graded doses of 10-100 µg of intracoronary nitroglycerin. The patients then received a 24-hour intravenous infusion of nitroglycerin (n = 12) or saline (n = 7). Repeat intracoronary instillation of the same doses of intracoronary nitroglycerin after the intravenous nitroglycerin infusion indicated a substantial reduction in coronary response: the percent increase in coronary sinus blood flow, which had been 30-52%, dropped to only 16–27%. In contrast, similar percent increases in coronary flow were noted before and after the intravenous saline infusion.

Attenuation of antiplatelet effect: Information obtained primarily from in vitro studies shows that nitrates affect platelet activity, although the clinical significance of these effects has not yet been determined. Nitrates prevent platelet aggregation, 10-13 disperse already formed platelet clumps, 11,14 and prevent platelet adhesion to damaged intimal linings.¹⁵ Interestingly, an in vitro study by Loscalzo and Amarante¹⁶ indicated that antiplatelet effects are also attenuated after prolonged exposure to nitroglycerin. When these investigators preincubated platelet-rich plasma in the absence of nitroglycerin, the median inhibitory concentration (IC₅₀) of nitroglycerin required for inhibition of adenosine diphosphate-induced platelet aggregation was approximately 40 μ M. When platelet-rich plasma was preincubated with nitroglycerin, the IC₅₀ increased 9-fold, to 360 μ M.

PROPOSED MECHANISMS OF NITRATE TOLERANCE

The precise cause of nitrate tolerance is still not entirely clear, but a number of mechanisms have been postulated. Among these are pharmacokinetic changes, depletion of sulfhydryl groups, the activation of neurohormonal vasoconstrictive mechanisms, and the expansion of intravascular volume.

Pharmacokinetic changes: A reduction in blood nitrate levels due to pharmacokinetic changes, such as alterations in drug absorption, distribution, or elimination, has been proposed as a mechanism for the diminishing effect of nitrate preparations over time. The feasibility of this explanation, however, is refuted by a recent study by Elkayam et al.¹⁷ The patients enrolled in this study demonstrated attenuation of the ISDNinduced reduction in PAWP within 24 hours after initiation of a 4-hour dosing regimen (Figure 2A). Despite the loss of clinical efficacy, plasma ISDN levels were significantly higher on the second day of dosing than on the first day (Figure 2B). The persistent elevation in blood levels of ISDN was, in fact, considered the probable cause of nitrate tolerance in these patients.

Depletion of sulfhydryl groups: Organic nitrates are prodrugs that must undergo biotransformation and activation in order to exert a clinical effect. This activation occurs via an interaction with sulfhydryl groups that is primarily intracellular but also occurs extracellularly (Figure 3). The products of this interaction, S-nitrosothiol and nitric oxide, then stimulate guanylate cyclase, the enzyme responsible for the formation of cyclic guanosine monophosphate (GMP). Cyclic GMP can, by a variety of mechanisms, lower the cytosolic free calcium and make contractile proteins less sensitive to calcium, an effect that eventually leads to vasodilation. Experimental evidence obtained both in vitro and in vivo lends support to the sulfhydryl depletion hypothesis of nitrate tolerance. Among the in vitro evidence is the decrease in the tissue content of sulfhydryl groups that occurs with prolonged exposure of vascular strips to nitroglycerin, which was first shown by Needleman¹⁸ as early as 1970 and then demonstrated in subsequent studies.^{19,20} In addition, there are several reports of the reversal of vascular tolerance after supplying sulfhydryl groups in the form of dithiothreitol and N-acetylcysteine (NAC). 19,21,22

Interestingly, one in vitro study showed that captopril, a sulfhydryl-containing angiotensin-converting enzyme (ACE) inhibitor, prevented the development of tolerance to the effect of nitroglycerin on aortic vascular rings.²³ Enalapril, a nonsulf-hydryl-containing ACE inhibitor, failed to prevent development of tolerance. Furthermore, only negligible tolerance has been seen with thiol-independent nitrate vasodilators, such as molsidomine and

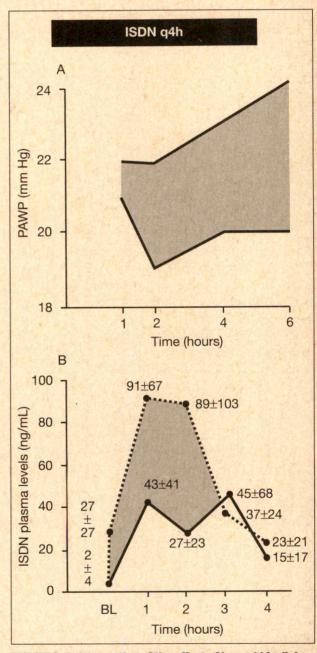


FIGURE 2. A, Attenuation of the effect of isosorbide dinitrate (ISDN) on pulmonary arterial wedge pressure (PAWP) with a 4-hour dosing regimen (q4h); n=11. B, Plasma ISDN levels achieved with a 4-hour dosing regimen; n=5. BL = baseline. (Adapted with permission from Circulation. 18)

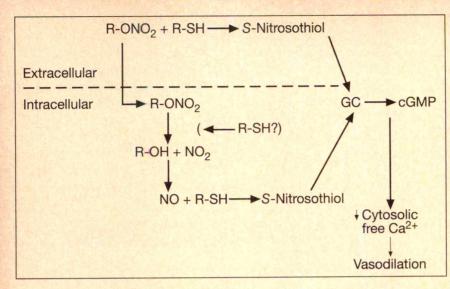


FIGURE 3. Role of sulfhydryl (SH) groups in nitrate(R-ONO₂)-induced vasodilation. GC = guanylate cyclase; cGMP = cyclic guanosine monophosphate; NO = nitric oxide.

nitroprusside, which do not require interaction with sulfhydryl groups for their effect.24,25 The same is true for the vasorelaxation induced by nitric oxide.26

In vivo evidence for the sulfhydryl depletion hypothesis includes the potentiation of the hemodynamic effects of nitroglycerin by the sulfhydryl group donor NAC. This effect has been observed in both rats and human beings. 27-30 Even more striking is the partial reversal of nitroglycerin tolerance in patients with congestive heart failure and coronary artery disease^{31,32} and in normal subjects³³ by sulfhydryl groups, supplied by either NAC or methionine.

In one study conducted by Packer et al31 in 35 patients with severe congestive heart failure, continuous intravenous infusion of nitroglycerin for 48 hours initially caused a statistically significant reduction in left ventricular filling pressure (LVFP) and mean right atrial pressure (MRAP). By the end of the treatment period, these effects were no longer present. The nitroglycerin-induced decrease in LVFP and MRAP was partially restored by administration of NAC.

Parker was unable to repeat the results in patients with angina pectoris who developed tolerance to ISDN, and he concluded that the interaction with NAC is drug-specific and does not occur with ISDN.34 However, in a recently completed study by Mehra et al35 in patients with congestive heart failure, the addition of NAC to ISDN augmented the nitrate-induced reduction in PAWP, indicating an interaction between ISDN and NAC.

Activation of neurohormonal vasoconstrictive mechanisms: The strong vasodilatory response to nitroprusside causes reflex stimulation of catecholamines and renin, resulting in vasoconstriction and at least a partial attenuation of the vasodilatory effect of nitroprusside. With abrupt discontinuation of nitroprusside, rebound vasoconstriction may also occur. It has been suggested that similar activation of neurohormonal vasoconstrictive mechanisms may play a role in the development of tolerance to nitrates.

The role of neurohormonal vasoconstrictive factors in the development of nitrate tolerance is supported by a number of reports of increased catecholamine levels or plasma renin activity in patients who develop nitrate tolerance. In the study mentioned above of patients with congestive heart failure conducted by Packer et al,31 plasma renin activity rose significantly, from 7.5 ± 2.9 ng/mL/hour at baseline to $12.9 \pm 4.8 ng/mL/hour$ after a continuous 48-hour infusion of nitroglycerin. In contrast, in patients receiving intermittent nitrate therapy, plasma renin activity showed a much smaller and statistically insignificant increase, from $6.1 \pm 2.7 \text{ ng/mL/hour before infusion}$ to $7.7 \pm 3.0 \text{ ng/mL/hour after infusion.}$

Expansion of intravascular volume: Several studies have shown that nitrate therapy is associated with either an expansion of plasma volume or an increase in body weight. This effect has been demonstrated in patients with myocardial infarction and congestive heart failure. 31,36,37

Dupuis et al, for example, reported a significant increase in blood volume of 745 ± 382 mL, primarily during the first hour of nitroglycerin therapy in patients with congestive heart failure.37 These patients showed no weight gain at that time, leading the investigators to propose a shift of fluid from the extravascular to the intravascular compartment as the cause of the augmented blood volume. An increase in blood volume is likely to attenuate the increase in venous capacitance initially observed with nitroglycerin.

CONCLUSION

The mechanisms responsible for the development of nitrate tolerance are not yet completely understood, although several possible hypotheses have been proposed. A combination of these various mechanisms is thought to be the most likely explanation for the development of tolerance to these drugs.

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DISCUSSION

Participant: Will diuretics restore sensitivity to nitrates?

Dr. Uri Elkayam: A preliminary report presented at a recent meeting indicated that nitrate tolerance might be prevented with diuretics in patients with angina. However, a paper that I reviewed recently from a group that has investigated nitrate tolerance intensively showed diuretics to have no effect on nitrate tolerance in normal volunteers. Thus, at this time, the effect of diuretics remains questionable.

Participant: There is a clear consensus that nitrate tolerance does develop. Is there tolerance to the anti-ischemic effect of nitrates, as manifested by the frequency of ischemic events recorded on 24-hour ambulatory monitoring?

Dr. Andrew P. Selwyn: Studies have shown that nitrates produce a consistent and modest decrease

in the frequency and duration of ischemia seen with 24-hour ambulatory monitoring, due primarily to a preferential decrease in episodes of ischemia occurring at lower heart rates of about 70-80 beats/min. That beneficial effect disappears by 24 hours. There are too few studies available to know whether intermittent application can preserve the effect on ischemic events observed during 24-hour ambulatory monitoring.

Dr. William H. Frishman: We have seen evidence of nitrate tolerance in terms of hemodynamic effects and exercise performance but not in terms of angina frequency, although that is not an objective criterion. Most studies suggest the persis-

tence of some anti-ischemic effect, particularly an effect on spontaneous attacks of angina.

Dr. Udho Thadani: There are published data showing that angina frequency and tolerance to the anti-ischemic effects develop with continuous transdermal nitroglycerin therapy in patients with a very high frequency of anginal attacks.

Dr. Jay N. Cohn: There is no question that continuous nitrate application and a constant blood level are most likely to produce tolerance. Although the optimal drug-free interval for maintaining efficacy is somewhat controversial, at least some efficacy is certainly maintained with intermittent regimens.

Rationale for Intermittent Nitrate Therapy

Ezra A. Amsterdam, MD

Tolerance to the pharmacologic and therapeutic effects of nitrate therapy is now well established. This phenomenon may be defined as either a decreased response to a given amount of nitrate or the need for an increased amount of nitrate to maintain a constant effect. Tolerance has been demonstrated with all forms of nitrate therapy that maintain continuous blood levels of the drug, including frequent oral dosing, constant intravenous infusion, and continuous transdermal delivery. It can develop rapidly after only a few doses of a nitrate preparation and tends to be partial rather than absolute. Strategies for the prevention of nitrate tolerance include the avoidance of maximum nitrate doses and the use of intermittent nitrate dosing regimens. Providing a relatively brief nitrate-free interval restores vascular responsiveness to nitrates, most likely due to a recovery of the metabolic mechanisms responsible for the therapeutic effect of these drugs. The duration of this period of nitrate abstinence varies, depending on the nitrate preparation used but is generally in the range of 8-12 hours. Such intermittent therapy not only reduces the risk of nitrate tolerance, but also provides a convenient approach to outpatient management.

(Am J Cardiol 1992;70:55G-60G)

olerance to the pharmacologic and therapeutic effects of nitrate therapy is now a wellestablished phenomenon. Nitrate tolerance is known to develop very rapidly and may occur after only a few doses of a nitrate preparation. It may be manifested as a decrease in patient response to a particular dosage or as a need for progressively higher doses to maintain the desired effect.

The "Monday morning headache" syndrome noted in nitrate factory workers provided the earliest evidence of nitrate tolerance.1 These headaches generally disappeared with nitrate exposure as the week progressed but returned the following Monday, after a nitroglycerin-free weekend. Tolerance has now been recognized with pharmacologic nitrate therapy as well. The development of tolerance to nitrate preparations is not limited to a specific route of administration but occurs with all forms of drug delivery that maintain continuous blood levels of the drug. By contrast, short-acting nitrate preparations such as sublingual tablets² and the spray form³ are not associated with tolerance during normal therapeutic use. Factors that have been recognized as important in the development of tolerance to nitrates include magnitude of the dose, frequency of administration, duration of therapy, plasma nitrate levels, and pharmacokinetic profile of the specific nitrate (Table I). Tolerance is not confined to a specific type of patient. It has been associated with treatment for both ischemic syndromes and congestive heart failure.

NITRATE TOLERANCE WITH ORAL, INTRAVENOUS, AND SUBLINGUAL **ADMINISTRATION**

Both definitions of nitrate tolerance—the reduced effect of a particular dosage and the need for higher doses to maintain efficacy—were illustrated by Thadani et al.4 This investigation was conducted in 12 patients with angina pectoris who were treated with placebo and oral doses of 15, 30, 60, and 120 mg of isosorbide dinitrate (ISDN). A single oral dose of ISDN produced a dose-related increase in treadmill walking time to the onset of

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TABLE I Factors Influencing Development of Nitrate Tolerance

- Dose
- Dosing interval
- Duration of therapy
- Plasma levels
- Pharmacokinetics

angina that persisted for up to 8 hours after administration (Figure 1). After several weeks of sustained therapy, the response to the various dose levels of ISDN was attenuated. Some therapeutic benefit was still apparent 1-2 hours postadministration, although the effect was less than that seen with acute therapy. After more than 2 hours, however, treadmill walking time with ISDN therapy was no different from that seen after administration of placebo. The unaltered dose of the drug, therefore, had a diminished clinical effect that was also of shorter duration.

A placebo-controlled study by Jugdutt and Warnica⁵ demonstrated the rapid development of tolerance to a modest dose of intravenous nitroglycerin in patients with acute myocardial infarction. This patient population required an increasing dose of nitroglycerin to achieve the desired hemodynamic effect, defined as a 10% decrease in mean blood pressure in normotensive patients and a 30% decrease in hypertensive patients. The initial mean infusion rate required to achieve the target blood pressure level was $45 \pm 34 \,\mu g/min$. Within a mean of 11 \pm 9 hours, an increase of 30 \pm 39 μ g/min was required to maintain the desired response.

Tolerance to intravenous nitroglycerin has also been observed in patients with congestive heart failure treated with a continuous infusion of the drug. Packer et al⁶ reported a favorable short-term effect of constant nitroglycerin infusion in 24 patients with severe chronic heart failure. After 2 hours of continuous nitroglycerin therapy, these patients demonstrated statistically significant increases in stroke-volume index and significant decreases in left ventricular (LV) filling pressure, mean arterial pressure, systemic vascular resistance, and mean right atrial pressure (MRAP). By 48 hours, however, mean arterial pressure, LV filling pressure, and MRAP had returned to pretreatment values, and the increases in strokevolume index and the decreases in systemic vascular resistance were markedly attenuated. The minimal change in mean arterial pressure, LV filling pressure, and MRAP following the discontinuation of nitroglycerin infusion provided further evidence of the loss of therapeutic efficacy.

May et al⁷ noted a diminished response of coronary sinus blood flow to continuous intracoronary infusion of nitroglycerin after 24 hours. Before the start of the infusion, study subjects, most of whom had coronary artery disease, demonstrated progressive increases in coronary sinus blood flow in response to graded doses of 10, 25, 50, and 100 µg of intracoronary nitroglycerin. A substantial reduction in this response occurred within 1 day of the start of nitroglycerin infusion.

Like oral ISDN and intravenous nitroglycerin therapy, transdermal nitrate delivery has also been

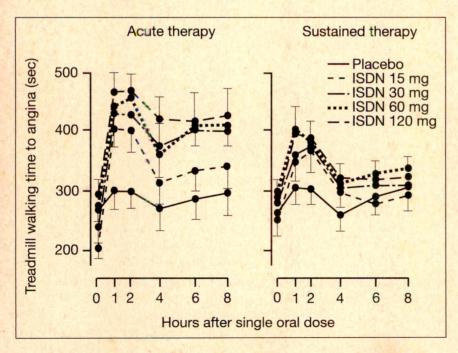


FIGURE 1. Duration of action of single oral doses of isosorbide dinitrate (ISDN) during acute (left) and sustained (right) therapy in 12 patients with angina. Results are mean ± standard error of the mean. (Adapted with permission from Am J Cardiol.4)

associated with the development of tolerance. In a double-blind, placebo-controlled crossover study by Parker and Fung,⁸ patients with chronic stable angina received sustained therapy with a nitroglycerin patch of 30 cm², which delivered approximately 15 mg of nitroglycerin over a period of 24 hours. After 1–2 weeks, treadmill walking times to the onset of angina and to the development of moderate angina were no different from values recorded during placebo therapy (Figure 2).

FEATURES OF NITRATE TOLERANCE

Fortunately, nitrate tolerance is generally partial rather than absolute, as demonstrated by data from several of the studies already described. In the trial by Jugdutt and Warnica,5 for example, mean blood pressure and the rate-pressure product between hour 12 and hour 48 did not differ substantially between nitroglycerin-treated and placebo-treated patients. Nevertheless, throughout the period of infusion, left ventricular (LV) asynergy, LV end-diastolic dimension and volume, and LV ejection fraction in patients receiving nitroglycerin were improved compared with values recorded in these same patients at baseline and with values recorded in a placebo treatment group. In addition, an analysis of data from individual patients indicated significant hemodynamic tolerance to nitroglycerin in only 37 (24%) of the 154 study subjects. The effect of the drug was maintained in the other patients.

Patients treated with a 24-hour infusion of nitroglycerin in the study by May et al did show some increase in coronary sinus blood flow in response to intracoronary nitroglycerin, although the percentage increase was smaller than that noted before the nitroglycerin infusion. At the initial evaluation, increases in coronary sinus blood flow ranged from approximately 25% with 10 µg of intracoronary nitroglycerin to nearly 50% with the 100 µg dose. After a 24-hour infusion of nitroglycerin, increases fell to between 20 and 30%.

As mentioned, Parker and Fung⁸ noted in their crossover study that treadmill walking time was similar during sustained transdermal therapy with an active 30 cm² nitroglycerin patch and during treatment with a placebo patch. However, despite the loss of the initial efficacy of transdermal nitroglycerin, patients still demonstrated a significant increase in walking time to the development of moderate angina in response to a 0.6 mg dose of sublingual nitroglycerin (see Figure 2).

Another feature of nitrate tolerance is its rapid disappearance. After a relatively brief period of

nitrate abstinence, responsiveness can usually be restored. In addition, tolerance does not develop with the use of sublingual preparations and nitroglycerin sprays that provide very abrupt rises and falls in blood drug levels. Intermittent dosing strategies that provide a nitrate-free interval may therefore be the key to the prevention of nitrate tolerance. Although the optimal period of abstinence has not yet been determined, it is likely to be relatively brief, and measured in hours. Such a dosing strategy may not only obviate the development of tolerance but also provide a practical approach to patient management.

INTERMITTENT NITRATE ADMINISTRATION TO CIRCUMVENT TOLERANCE

Data obtained in clinical investigations support the value of intermittent nitrate administration as a means of preventing the development of nitrate tolerance. Parker et al⁹ evaluated the effect of sustained therapy with a daily dose of 30 mg of ISDN given according to 3 different dosing schedules in patients with angina. Patients treated with an ISDN regimen 4 times daily showed some improvement in treadmill walking time to the onset of angina and the development of moderate angina at 1 hour following drug administration (Figure 3). At the 3- and 5-hour postdose evaluations, however, these values did not differ significantly from those in patients treated with placebo. In contrast, a beneficial effect relative to placebo was apparent

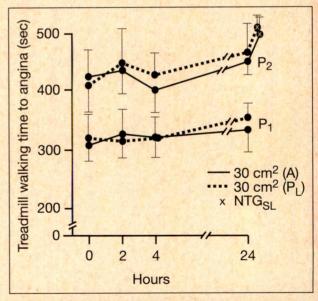


FIGURE 2. Treadmill walking time (TWT) (standard error of the mean) to the onset of angina (P_1) and the development of moderate angina (P_2) in patients treated with an active nitroglycerin patch, 30 cm² (A), and a placebo patch (P_L) and in response to sublingual nitroglycerin (NTG_{SL}). (Adapted with permission from Am J Cardiol.8)

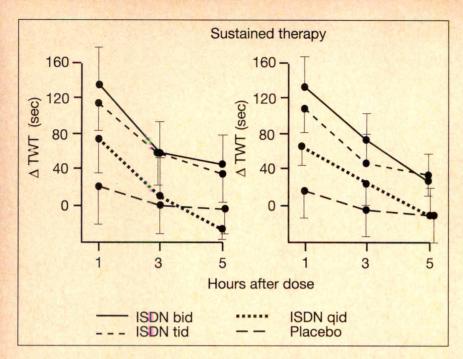


FIGURE 3. Changes from control values in treadmill walking time (TWT) to the onset of angina (left) and the development of moderate angina (right) during sustained therapy with 30 mg isosorbide dinitrate (ISDN) given 2 (b.i.d.), 3 (t.i.d.), and 4 (q.i.d.) times daily. (Adapted with permission from N Engl J Med.9)

at all evaluation periods in patients receiving ISDN 2 or 3 times daily.

As indicated before, heart failure patients treated by Packer et al with a continuous infusion of nitroglycerin gained immediate hemodynamic benefits but became tolerant to the drug within 48 hours. With intermittent infusion of nitroglycerin, however, the initial positive effects of the drug on LV filling pressure, MRAP, mean arterial pressure, systemic vascular resistance, and strokevolume were maintained. When intermittent nitroglycerin was discontinued, these drug-induced effects were reversed. This return to pretreatment values did not occur when the continuous infusion

was stopped, because efficacy had already been lost.

An intermittent dosing strategy also appears to be effective in preventing tolerance to transdermal nitrate therapy, as reported by DeMots and Glasser. 10 These investigators evaluated the response of angina patients to various sizes of nitroglycerin patches, ranging from 10-40 cm,² that were worn continuously for a 12-hour period and then removed for a 12-hour drug-free interval. After 1 month of therapy, the increase in time to moderate angina that had been observed on the first day of therapy was maintained with the larger nitrate patches of 30 and 40 cm² (Figure 4).

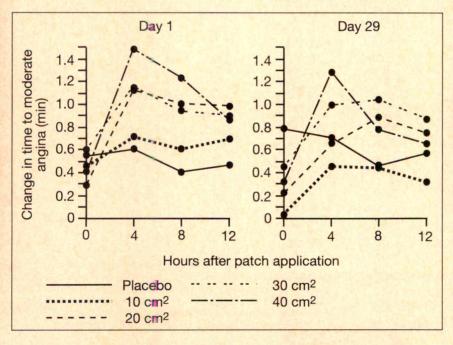


FIGURE 4. Mean changes from baseline in time to the development of moderate angina in patients treated with various individual doses of transdermal nitroglycerin. (Adapted with permission from J Am Coll Cardiol. 10)

CLINICAL CONSIDERATIONS WITH INTERMITTENT NITRATE THERAPY

The data obtained in the foregoing studies indicate that intermittent nitrate therapy can provide an effective and practical approach to the management of ambulatory outpatients. Such an intermittent dosing strategy is believed to allow time for the recovery of the mechanisms responsible for the therapeutic effect of nitrates. The optimal duration of the nitrate-free interval is still under investigation. The information available at this time, however, suggests that a period of abstinence of more than 8 hours is needed to maintain responsiveness to nitrates.

The appropriate nitrate-free interval in patients receiving intravenous nitroglycerin is unclear and appears to be dependent on both the dose and the duration of therapy. Furthermore, continuous therapy is generally desirable in the types of patients receiving intravenous nitroglycerin, such as those with unstable angina. The fact that nitrate tolerance is partial rather than absolute would appear to play an important role in the successful management of these patients. Constant infusion of nitroglycerin is likely to continue to provide some benefit, even though the effect may diminish over time. Large increases in the nitroglycerin dose should also help maintain efficacy in these patients until definitive therapy can be initiated.

Another concern with the use of intermittent nitrate dosing strategies is the potential for breakthrough symptoms to occur during the period of nitrate withdrawal. In some cases symptoms may actually be worse toward the end of the dosing interval than before the start of nitrate therapy, a phenomenon that has been termed the "zero-hour effect."11 These breakthrough or rebound effects have not presented significant problems in clinical practice, largely because very few patients receive nitrates as monotherapy. Rather, most patients with ischemic heart disease or heart failure also receive concomitant therapy with other agents, such as β blockers or calcium antagonists; thus, nitrate tolerance is not always recognized.

The development of nitrate tolerance during intermittent therapy may not invariably result in the recurrence of symptoms but may be manifested in subclinical form, such as episodes of silent ischemia. Consequently, monitoring the frequency of both symptomatic and silent ischemia may be advisable during the nitrate-free interval. The findings can then be used to adjust therapy so as to maintain the therapeutic efficacy of the nitrate preparation.

Other approaches to obviate nitrate tolerance have included treatment with a sulfhydryl donor, such as N-acetylcysteine. 12 Results of this method have been inconsistent.¹³ Non-sulfhydryl mechanisms, such as activation of neurohumoral factors and increase in blood volume, have also been considered to play a role in the development of nitrate tolerance.9

CONCLUSION

It is important that physicians be aware of the potential for tolerance to develop in patients receiving nitrate therapy. Tolerance can usually be managed by adjustments in the dosing strategy or a change in the type of nitrate prescribed. Avoidance of maximum nitrate doses and the incorporation of a nitrate-free interval into the dosing schedule are among the measures that should be helpful in reducing the occurrence of nitrate tolerance.

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DISCUSSION

Dr. Richard Gorlin: Would you recommend a morning dose of nitroglycerin followed 4-6 hours later by a higher afternoon dose and then a nighttime nitrate-free interval for a patient with stable angina?

Dr. Ezra A. Amsterdam: That is an interesting approach, but its effectiveness must be evaluated

on an individual basis. For instance, such a regimen would be appropriate for a patient who is experiencing more angina during the late hours of the day or who is more active in the afternoon.

In the past, angina was thought to occur infrequently during the night, and nighttime therapy was therefore considered to be unnecessary. During the past few years, we have become aware that patients may develop nocturnal angina as nitrate levels fall and protection decreases. In fact, in some patients it may be advisable to reverse the period of active nitrate therapy and the nitrate-free interval, against a background of concomitant therapy. Although general guidelines for the use of nitrates have been developed, the optimal dosing strategy must be determined on an individual basis.

Participant: You have associated this nitratefree interval with the potential for both breakthrough symptoms and rebound. Do you believe that long-acting forms of nitroglycerin should never be used alone for the management of angina?

Dr. Amsterdam: You must remember that breakthrough symptoms were seen in a subgroup of patients. If you are uncertain about the risk of breakthrough, that might be a very helpful admonition. Breakthrough may be symptomatic or may be manifested as silent ischemic episodes, which are now considered to be clinically important. To ensure that breakthrough is not occurring, you must do more than question your patient about symptoms. If you are unsure as to whether this is occurring, it is reasonable to avoid monotherapy.

Pharmacokinetics of Isosorbide Mononitrate

Ulrich W.P. Abshagen, MD

Pharmacokinetic studies show that isosorbide mononitrate is rapidly absorbed after oral administration, reaches peak concentrations within an hour, undergoes no significant first-pass metabolism, and is virtually 100% bioavailable. The halflife is approximately 5 hours, the volume of distribution is 0.62 liter/kg, and the systemic clearance is 115 mL/min. Only 1-2% of an orally administered dose is excreted unchanged in the urine, with the remainder being eliminated as inactive metabolites. Isosorbide mononitrate follows dose-linear kinetics after single and multiple doses. Its pharmacokinetic profile is consistent and highly reproducible and is unchanged in the elderly and in patients with coronary artery disease, renal failure, or liver cirrhosis. An asymmetrical dosage regimen of isosorbide mononitrate has been shown to provide antianginal efficacy for at least 12 hours. Because asymmetrical dosing creates irregular, sawtooth-like changes in plasma concentrations and a fall below a critical threshold level during the night, tolerance does not develop.

(Am J Cardiol 1992;70:61G-66G)

he conception and subsequent development of isosorbide mononitrate as an antianginal agent was prompted by a provocative overstatement exactly 20 years ago by the U.S. pharmacologist Philip Needleman, who contributed so much to the field of nitrate pharmacology and biochemistry. Needleman found that nitrate doses that effectively lowered blood pressure when injected into the jugular vein in rats had no effect when injected into the portal vein.1 On the basis of these experiments, he claimed that oral therapy with organic nitrates was a placebo.

Although such a blanket statement would seem ludicrous to us today, Needleman was actually correct in pinpointing a critical pharmacologic weakness of the oral nitrates that were available at that time: all were subject to very high first-pass extraction through the liver. For example, the first-pass extraction of nitroglycerin is more than 95%, so that less than 5% of an administered dose reaches the systemic circulation after oral administration. In the case of isosorbide dinitrate, 70-80% of a given oral dose is degraded by the first pass through the liver.

These observations stimulated intensive investigation into the first-pass metabolism and vasoactivity of isosorbide dinitrate and its metabolites. We knew that the principal metabolic degradation reaction was denitration and that the affinity of hepatic enzyme glutathione S-transferase was highest for the dinitrate, lower for the 2-mononitrate metabolite, and lowest for the 5-mononitrate metabolite. Our working hypothesis was that first-pass metabolism should follow the same sequence, and, indeed, we found that the 5-mononitrate persisted in plasma for many hours after the disappearance of the parent compound. First-pass extraction of the 5-mononitrate was less than 5%, making this compound the only oral nitrate to be nearly 100% bioavailable. The negligible first-pass extraction more than compensated for the lower intrinsic vasoactivity of the metabolite, relative to the parent compound.

Once the oral bioavailability of isosorbide mononitrate was established, the century-old controversy over the development of nitrate tolerance

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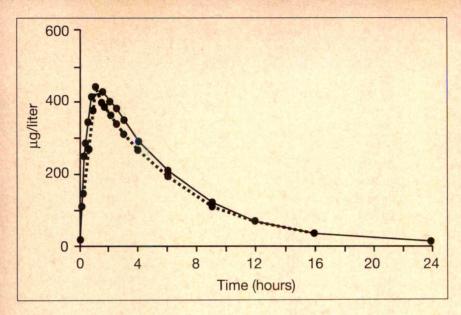


FIGURE 1. Mean concentrations of isosorbide-5-mononitrate in plasma: intravenous (IV) infusion versus oral administration. ---IV infusion (20 mg for 1 hour; n = 11) --- = oral dose (20 mg: n = 20). (Adapted with permission from Eur J Clin Pharmacol.2)

remained to be addressed. Since the determinant of tolerance development is continuously high concentrations, we performed intensive studies in chronically instrumented conscious dogs in which we varied the half-life and the dosing interval. On the basis of these studies, we were able to design a rational dosage regimen that would minimize the development of tolerance in patients.

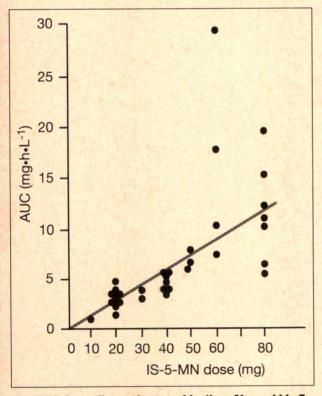


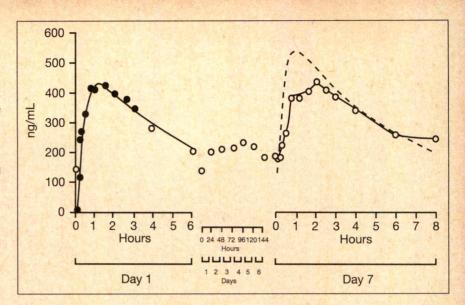
FIGURE 2. Dose-linear pharmacokinetics of isosorbide-5mononitrate (IS-5-MN). Total areas under the plasma concentration curves (AUC) after single oral doses of IS-5-MN: in healthy volunteers (10-50 mg); patients with New York Heart Association class III cardiac failure (60 mg); and coronary patients (80 mg). (Adapted with permission from Springer Verlag.7)

PHARMACOKINETIC PROFILE

Absorption, distribution, clearance: The plasma concentration-time curve following intravenous infusion of 20 mg isosorbide mononitrate over 1 hour is virtually superimposable on the curve that follows oral administration of the same dose (Figure 1).² This superimposability signifies 100% bioavailability and the absence of any firstpass metabolism. The elimination half-life of the mononitrate is approximately 5 hours. Isosorbide mononitrate is absorbed rapidly, with maximum concentrations being reached within 60 minutes of oral administration. The volume of distribution is approximately the volume of total body water (0.6 liter/kg), which is considerably smaller than that of the more lipophilic compounds isosorbide dinitrate and nitroglycerin. Total body clearance is 115-120 mL/min, and plasma protein binding is negligible.

Metabolism: Only about 2% of an administered dose is excreted unchanged in the urine within 24 hours after oral administration of a 20 mg dose.3 Approximately 30% is excreted as isosorbide, which has an elimination half-life of 8 hours, and 17% as the 2-glucuronide of the mononitrate, which has an elimination half-life of 6 hours.4 The high renal clearance of the 2-glucuronide (1.8 liters/min) provides evidence for intrarenal glucuronidation as the major form of metabolism.5 The remainder of the mononitrate dose is presumably further degraded to sorbitol and other compounds. None of these metabolites is vasoactive, which means that

FIGURE 3. Mean plasma concentrations (ng/mL) of isosorbide-5mononitrate (IS-5-MN) in patients with coronary artery disease given 20 mg IS-5-MN 3 times daily during 1 week (open circles; n = 18) versus mean plasma concentrations after a single oral dose in young healthy volunteers (solid circles; n = 20). The dashed line represents a computer simulation curve of the expected values during steady state, demonstrating dose-linear kinetics of IS-5-MN after multiple as well as after single dosing. (Adapted with permission from Med Welt.9)



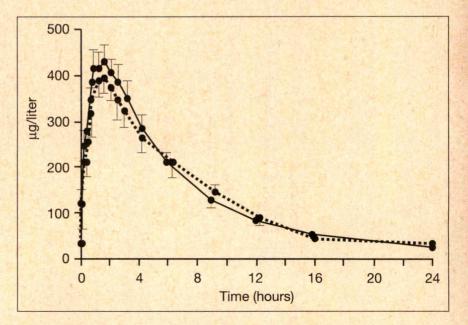
after isosorbide mononitrate is administered, only one active compound is present and that compound is nearly 100% bioavailable. This metabolic pattern contrasts with the more complicated pharmacokinetics seen during chronic therapy with other nitrates, when a variable mixture of metabolites with different activities is present. For example, it has been pointed out that during long-term treatment with nitroglycerin, an accumulation of active metabolites contributes progressively more to the drug's effects, so that plasma nitroglycerin levels do not fully reflect total drug activity in the body.⁶

Kinetics at different single doses: To ascertain whether isosorbide mononitrate follows doselinear kinetics, we compiled data from different studies and plotted the areas under the plasma concentration curves (AUCs) against the doses

(10–80 mg) used (Figure 2).⁷ This revealed a perfect linear relation following single oral doses of isosorbide mononitrate.

Kinetics after multiple dosing: Isosorbide dinitrate follows dose–linear kinetics after single doses but deviates from linearity during chronic therapy as a result of competitive inhibition of the enzyme glutathione S-transferase by the drug's metabolites. This finding raised the issue of whether the dose linearity of isosorbide mononitrate would also hold under chronic conditions. To answer this question, plasma isosorbide mononitrate concentrations were measured during a week-long course of therapy with 20 mg 3 times daily in 18 patients with coronary artery disease. The plasma levels within one dosage interval during steady state proved to be similar to the plasma levels following a single oral dose of 20 mg in healthy young volunteers

FIGURE 4. Serum concentrations versus time of isosorbide-5-mononitrate (IS-5-MN) in patients with renal failure, following oral administration of 20 mg IS-5-MN. --- = healthy volunteers (n = 20); . . . = patients with renal failure (creatinine clearance 4.3–40.5 mL/min; n = 20). (Adapted with permission from Med Welt. 10)



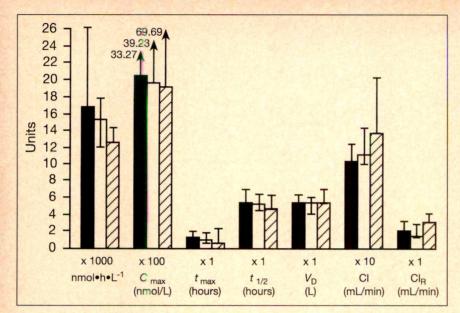


FIGURE 5. Kinetic parameters of isosorbide-5-mononitrate (IS-5-MN) in patients with liver cirrhosis and in normal subjects: intravenous (IV) and oral (po) doses of 20 mg IS-5-MN. Columns repre sent median values: vertical lines indicate the range. The factor for conversion of the units on the ordinate into the correct value of each parameter is given on the abscissa. C_{max} = maximum plasma concentration; tmax = time to C_{max} ; $t_{1/2} = \text{plasma half-}$ life; V_d = volume of distribution; CI = clearance; CI_R = renal clearance; = i.v. liver patients n = 6, □ = p.o. liver patients N = 6; □ = p.o. volunteers N = 6. (Adapted with permission from Akpan et

(Figure 3).9 These results indicated that isosorbide mononitrate follows dose-linear kinetics after multiple as well as after single dosing.

Pharmacokinetic variability: Because isosorbide mononitrate is completely absorbed and does not undergo first-pass metabolism, its pharmacokinetic parameters are highly reproducible. The coefficients of variation of mean plasma concentrations and related pharmacokinetic parameters are low and do not exceed 18-20% after single and multiple dosing.^{2,9}

Influence of age, renal impairment, and cirrhosis on pharmacokinetics: There are no age-related differences in the pharmacokinetics of isosorbide mononitrate.9 This is an important consideration, given that many patients with angina are elderly.

Since isosorbide mononitrate is eliminated by metabolism and only negligible amounts appear in the urine, no alterations in pharmacokinetics are seen in renal impairment, even at creatinine clearances as low as 4.3 mL/min (Figure 4).¹⁰

The pharmacokinetics of isosorbide mononitrate are also unchanged in patients with biopsyproven cirrhosis and gross decreases in antipyrine clearance (Figure 5).11 We also saw no effect on concentration-time course and AUC in a patient who underwent an end-to-side portacaval shunt operation. This is in contrast to what has been reported with nitroglycerin, the metabolism of

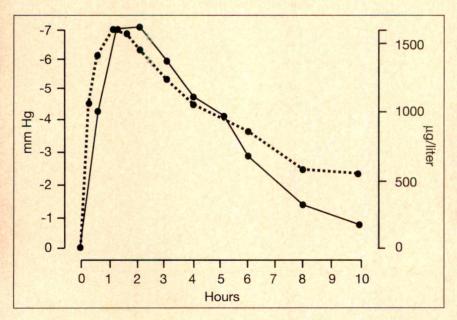


FIGURE 6. Plasma levels of isosorbide mononitrate (IS-5-MN, μg/liter; --) and pulmonary capillary wedge pressure changes (mm Hg; . . .) in patients with acute myocardial infarction who were given a single oral dose of 80 mg IS-5-MN. (Adapted with permission from Med Welt. 13)

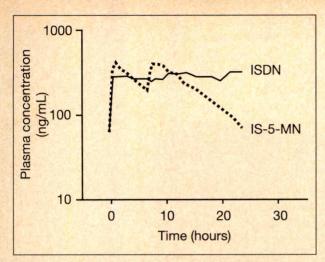


FIGURE 7. Mean steady-state plasma concentrations after 4 days of asymmetrical dosing with isosorbide-5-mononitrate (IS-5-MN) 20 mg twice daily (---) or sustained-release isosorbide dinitrate (ISDN) 40 mg 3 times daily (....). (Adapted with permission from Springer Verlag.)

which is more complex and intensive. Using digital plethysmography, Porchet and Bircher¹² showed that in cirrhotic patients with an end-to-side anastomosis, the bioavailability of nitroglycerin increased from 2% to 100%.

Correlation between plasma concentrations and effects: The pharmacokinetic profile of isosorbide mononitrate is simple, consistent in different populations, and highly predictable in clinical use. Thus, we can expect a clear correlation between the dose administered, the plasma concentration achieved, and the response elicited. An example is shown in Figure 6, where the time course of the decrease in pulmonary capillary wedge pressure closely follows the time course of plasma isosorbide mononitrate concentrations in patients with acute myocardial infarction. 13

AVOIDING TOLERANCE: THE SAW-TOOTHED PHENOMENON

Another key issue is whether the development of tolerance can be avoided during chronic oral nitrate therapy. Using an asymmetrical dosage regimen (20 mg given at hours 0 and 7), isosorbide mononitrate has provided antianginal efficacy for at least 12 hours as demonstrated by exercise stress testing.¹⁴ In a separate pharmacokinetics study using the same dosage regimen of isosorbide mononitrate, mean plasma concentrations were 60-400 mg/mL.¹⁵ Because asymmetrical dosing creates irregular, saw-toothedlike changes in plasma concentrations and a fall below a critical threshold level during the night, tolerance to isosorbide mononitrate does not develop. Figure 7 shows the

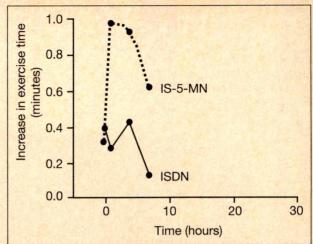


FIGURE 8. Increase in exercise time during therapy with isosorbide-5-mononitrate (IS-5-MN, 20 mg twice daily) asymmetrical dosing or isosorbide dinitrate (ISDN, 40 mg 3 times daily), compared with placebo. (Data from J Invas Cardiol.16)

contrast between the saw-toothed phenomenon following 4 days of asymmetrical dosing with isosorbide mononitrate and the nearly flat, continuous, steady-state plasma levels of the mononitrate following therapy with sustained-release isosorbide dinitrate, 40 mg 3 times daily.15 This difference translates into improved exercise time during chronic therapy with isosorbide mononitrate compared with the dinitrate (Figure 8).16

CONCLUSION

Isosorbide mononitrate has a straightforward pharmacokinetic profile, virtually 100% bioavailability, and dose-linear kinetics. The pharmacokinetics of the drug are not altered in elderly individuals or in patients with coronary heart disease, renal failure, or hepatic dysfunction. The use of asymmetrical dosing regimens circumvents the problem of tolerance during long-term antiischemic therapy by enabling the nitrate receptors to regenerate or compensatory mechanisms to come into play. In addition, we can provide patients with an antianginal agent that approximates physiologic replacement therapy, since endothelium-derived relaxing factor is most likely nitric oxide, which is the active principle of nitrates.

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DISCUSSION

- Dr. Uri Elkayam: We have been measuring the concentrations of isosorbide-5-mononitrate after the administration of isosorbide dinitrate to patients with heart failure, and it is clear that there is no hemodynamic correlation with the levels of the metabolites. Is this because the levels of the metabolites are too low?
- Dr. Ulrich W.P. Abshagen: It is difficult to show a relationship because of the presence of 3 moieties—isosorbide dinitrate, isosorbide-2-mononitrate, and isosorbide-5-mononitrate—with different intrinsic vasoactivity and different kinetics. Demonstration of a relation during chronic therapy would require weighting the contributions of the 3 active moieties in a superimposed model. Since only 1 active moiety is present during isosorbide mononitrate therapy, you have a clearer picture that can be more readily correlated with the hemodynamic effects.
- Dr. Uri Elkayam: Do you have information on the pharmacokinetics of isosorbide mononitrate in patients with severe congestive heart failure?
- Dr. Abshagen: The data show that the pharmacokinetics of isosorbide mononitrate in patients with New York Heart Association class III or IV heart failure do not differ from what is seen in normal subjects.1

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Efficacy of Isosorbide Mononitrate in Angina Pectoris

Udho Thadani, MBBS, MRCP, FRCP(C), FRS, and Philip J. de Vane, MD

The rapid development of tolerance has limited the applicability of oral and transdermal nitrates in the long-term management of patients with chronic stable angina pectoris. Recent well-controlled trials have demonstrated that asymmetrical, or eccentric, dosing of oral isosorbide mononitrate, in which 20-mg doses are taken at 8 A.M. and 3 p.m., provides at least 12 hours of antianginal coverage. There is no evidence for the development of tolerance with this schedule, which allows for a 17-hour nitrate withdrawal period. Likewise, the asymmetrical 20-mg twice daily regimen has not been associated with the zerohour effect that has been reported with higher oral doses of isosorbide mononitrate and with intermittent nitroglycerin patch therapy. This approach also avoids the development of a clinical rebound phenomenon, as measured by increased episodes of angina and nitroglycerin consumption, compared with the pretreatment period, during the nitrate-free interval at night and the early hours of the morning.

(Am J Cardiol 1992;70:67G-71G)

he main limitation of long-term prophylactic nitrate therapy for angina pectoris has been the development of tolerance, which may render these agents ineffective. 1-5 Isosorbide mononitrate, an active metabolite of isosorbide dinitrate, has been proved in clinical trials to be an effective antianginal compound that can be administered twice daily with the development of little or no tolerance over the long term. Recent evidence, reviewed here, supports the utility of an asymmetrical, or eccentric, dosing schedule in providing antianginal and anti-ischemic benefit for at least 12 hours, with efficacy sustained during chronic therapy.

THE CHALLENGE OF TOLERANCE: HISTORICAL BACKGROUND

When the development of tolerance was first linked to chronic oral therapy with isosorbide dinitrate, it was suggested that an 8- or 10-hour nitrate-free interval might avoid this problem. However, early studies by Thadani et al1 showed that during four times daily therapy with isosorbide dinitrate, the last dose of medication, taken 10 hours prior to the morning dose, was insufficient to prevent tolerance, and the morning dose provided efficacy for only 1-2 hours.

Subsequent studies showed that tolerance to the circulatory and antianginal effects of transdermal nitroglycerin patches developed within 24 hours of patch application.⁶ At 4 hours, there were significant increases in total exercise time (456 seconds with the patch versus 338 seconds with placebo) and in duration of exercise to the onset of angina (383 versus 257 seconds) and significant decreases in ST-segment depression (0.6 mm with the patch versus 1.0 mm with placebo), but these improvements were not sustained at 24 and 48 hours. 6 This attenuation of drug effect occurred despite stable plasma concentrations and irrespective of patch

In subsequent studies, a sustained-release formulation of isosorbide-5-mononitrate was used to determine the duration of drug effect and its

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relationship to plasma concentration during a course of once-a-day therapy. Both 50 mg and 100 mg were effective in increasing exercise time to the onset of angina and total exercise duration at 4 hours after the first dose, but not at 20 or 24 hours. However, after 1 week of therapy in this crossover study, antianginal and anti-ischemic effects were lost, even at 4 hours after dosing. Although plasma drug concentrations declined progressively over time, they remained consistently within the therapeutic range.

These findings raised the possibility that the development of tolerance might be avoided by the administration of smaller doses twice daily to achieve fluctuating plasma drug levels and ensure a relatively low drug concentration before the morning dose. Thadani et al8 therefore conducted a double-blind, randomized, crossover trial to evaluate the efficacy of 20 and 40 mg of isosorbide-5mononitrate given every 12 hours. They found significant increases in exercise duration 2 and 6 hours after the first dose. After 1 week of the twice-daily regimen, however, the 2-hour peak effect was reduced, and no significant increase in exercise duration could be demonstrated at 6 or 10 hours, despite higher plasma drug concentrations. Thus, treatment at 12-hour intervals was associated with the development of partial tolerance.

Other studies likewise pointed to a risk of tolerance with continuous treatment. A doubleblind crossover study by Cowan et al9 indicated that any improvements in exercise time and decreases in ST segment depression were lost after 1 week of continuous patch treatment. In contrast, with an intermittent therapy regimen, in which patients received a 10-mg patch at 8 A.M. and a placebo patch at 8 P.M., the beneficial effects were maintained and tolerance did not develop.

The rationale for current 2- and 3-times-a-day dosing schedules for isosorbide dinitrate was provided by a study of 12 patients conducted by Parker et al. 10 In this study, increases in exercise duration relative to placebo remained statistically significant 1, 3, and 5 hours after dosing, despite some attenuation as compared with the first dose. However, a more recent study by Bassan¹¹ has shown that long-term therapy with isosorbide dinitrate 3 times daily yields, at best, 6 hours of antianginal efficacy during a 24-hour interval, with the magnitude of the effect declining with each successive dose during the day. According to the results of this study, exercise time increased 1 hour after the daily 8 A.M. and 1 P.M. doses but returned to control levels within 3 hours of each dose. After the third

daily dose, virtually no increase in exercise time could be demonstrated. Thus, the conventional 3-times-daily regimen of isosorbide dinitrate, used confidently by so many physicians, actually affords only limited protection against effort-induced angina.

CLINICAL TRIALS OF ISOSORBIDE MONONITRATE

The development process for isosorbide mononitrate has mirrored the continuing controversies about nitrate therapy. The major issues have included not only efficacy, safety, duration of effect, and tolerance but also 2 concerns related to intermittent dosing schedules: time-zero (or zero-hour) effects and rebound. Time-zero refers to a worsening in exercise performance on a stress test just before the morning dose of the active medication (hence zero-hour) relative to the performance at the same time during placebo therapy. Rebound is an increase in angina attacks during the withdrawal period compared with the pretherapy period, particularly in the early morning hours.

The clinical utility of isosorbide mononitrate was established in 5 controlled studies involving a total of 473 patients with angina pectoris. In all of these studies, stress test data were obtained before dosing and at 1, 4, and 7 hours after dosing, following a single dose, and after 2 or 3 weeks of chronic therapy; one study obtained data for the afternoon (at 2 and 5 hours after dosing) as well as the morning dose. Primary efficacy, secondary efficacy, and duration of effect were evaluated. The primary efficacy variable was peak effect, defined as the longest time to moderately severe angina during stress tests at any of the time points. Secondary efficacy was determined as the time to moderately severe angina during the stress tests conducted at the designated hours after the morning or afternoon dose, and duration of effect was measured at the stress test 7 hours after the morning dose or 5 hours following the afternoon

Tolerance and time-zero effects at different dose levels: An early placebo-controlled study of asymmetrical dosing revealed a time-zero effect with a 60-mg dose but not with a 40-mg or 20-mg dose (unpublished data). In addition, although higher plasma drug levels were achieved with 40-mg and 60-mg doses than with the 20-mg dose, the higher doses offered little advantage in terms of clinical efficacy and were associated with a less favorable safety profile. Evidence of efficacy was weaker for the 60-mg dose than for either the 20or the 40-mg dose. The clear attenuation of effect with higher doses suggests tolerance is a function not only of the dosing schedule but also of the dose levels attained.

A subsequent study demonstrated that exercise performance was significantly greater after single doses of either 10 or 20 mg of isosorbide mononitrate than after placebo (unpublished data). The data suggested slight superiority of the 20-mg dose over a 10-mg dose after multiple dosing. A timezero effect was noted with the 10-mg dose but not with the 20-mg dose. The results of this study must be viewed with caution, however, in light of the finding of statistically significant treatment group-by-center effects.

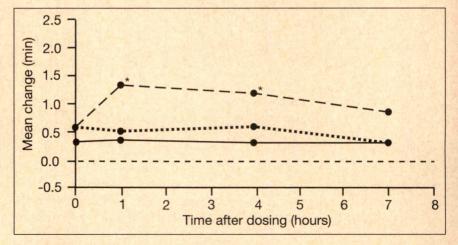
Asymmetrical twice-daily isosorbide mononitrate versus conventional 3-times-daily isosorbide dinitrate: A pivotal study¹² compared the effects of isosorbide mononitrate, 20 mg given asymmetrically at 8 A.M. and 3 P.M., and the effects of a standard regimen of sustained-release isosorbide dinitrate, 40 mg taken at 8 A.M., 3 P.M., and 10 P.M., with the effects of placebo. The eccentric mononitrate schedule resulted in statistically significant increases in mean time to moderately severe anginal pain at the time of peak effect and 1 and 4 hours after drug administration, in comparison with placebo. This clinical benefit persisted throughout the entire dosing interval, even after chronic treatment (Figure 1). In contrast, as Figure 1 also shows, after only 2 weeks of treatment, the dinitrate was no different from placebo in terms of increasing exercise time. The diminution of efficacy after multiple doses of isosorbide dinitrate given 3 times a day is consistent with the development of tolerance. No time-zero effect was noted in either treatment group.

Eccentric versus "concentric" isosorbide mononitrate: The superiority of unconventional isosorbide mononitrate dosing was conclusively

established in a trial comparing an eccentric twice-daily regimen (20 mg at 8 A.M. and 3 P.M.) with a "concentric" twice-daily regimen (20 mg at 8 A.M. and 8 P.M.). Although, during chronic therapy, both dosing schedules were effective relative to placebo 1 hour after dosing, only with the eccentric regimen was efficacy sustained at 4 hours. This trial and a prevously cited report also underscored 2 limitations of the conventional twice-daily regimen: it neither provides antianginal coverage for 12 hours nor affords a nitrate-free interval that is long enough to prevent the development of tolerance.

Duration of efficacy with eccentric dosing: The next step was to confirm the efficacy of the second daily asymmetrical dose during chronic therapy and to make sure that eccentric dosing does not pose the risk of rebound or time-zero effects on exercise tolerance. To address these questions, a multicenter, double-blind, placebocontrolled study was conducted, involving 116 patients with exercise-induced stable angina.¹⁴ After 2 weeks of therapy, the improvement in exercise tolerance at 2 hours, 5 hours, and 7 hours after the morning dose was significantly greater (p < 0.05) than that seen with placebo (Figure 2). The superiority of the drug to placebo was also evident just before the morning dose, indicating the absence of a zero-hour effect. Total exercise time was also significantly improved, relative to placebo, 2 hours and 5 hours after the afternoon dose (Figure 2). An interesting observation with both active drug and placebo was a decline in evening exercise performance, which may have been a postprandial phenomenon, fatigue after multiple exercise tolerance tests, or diurnal variation. The peak changes in total exercise time were nearly identical after the morning and afternoon doses. Although total exercise time achieved after the afternoon dose was slightly less than that seen with the morning dose,

FIGURE 1. Time to moderately severe anginal pain, expressed as change from pretherapy, with isosorbide mononitrate (IS-5-MN), 20 mg given at 8 A.M. and 3 P.M., and sustained-release isosorbide dinitrate (ISDN), 40 mg taken at 8 A.M., 3 P.M., and 10 P.M. --- IS-5-MN, 20 mg; --- ISDN, 40 mg; --- placebo. *p < 0.05. (Adapted from J Invasive Cardiol. 12)



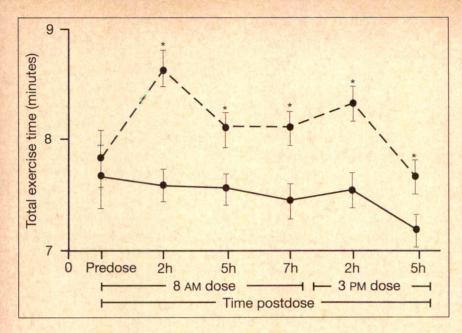


FIGURE 2. Change in total exercise time during chronic therapy with an asymmetrical twice-daily regimen of isosorbide mononitrate (IS-5-MN). --- = IS-5-MN; --- = placebo. *p < 0.05. (Adapted from Circulation.14)

this reduction in activity was not clinically significant as assessed by exercise tolerance testing. Total exercise time was also lower after the afternoon dose than after the morning dose in the placebo group. Clinical benefit was thus maintained, despite an apparent attenuation in exercise time after the afternoon dose.

To monitor the possible occurrence of angina attacks during the nighttime nitrate withdrawal interval, patients were asked to note any such attacks in a diary. These records evinced no statistically significant difference between active treatment and placebo in the number of nocturnal attacks. Thus, asymmetrical twice-daily therapy was associated with no rebound increase in anginal attacks during the night or early hours of the morning.

It should be pointed out that 50% of the patients in this study were receiving a β blocker.¹⁴ Although the sample size was too small to permit meaningful conclusions, there was nevertheless a suggestion of benefit with combination therapy in those in whom exercise tolerance was limited owing to angina, despite β blocker therapy.

CONCLUSION

Well-controlled trials have demonstrated that oral isosorbide mononitrate, 20 mg twice daily, is an effective antianginal agent. An asymmetrical dosing regimen, in which the drug is taken at 8 A.M. and 3 P.M., allows for a 17-hour nitrate withdrawal period and provides at least 12 hours of clinical benefit. Although higher doses have been implicated in causing tolerance, there is no evidence for the development of tolerance with 20 or 40 mg of isosorbide mononitrate given in an asymmetrical dosing schedule that includes a 17-hour withdrawal period. Likewise, the 20- or 40-mg asymmetrical twice-daily schedule has not been associated with the zero-hour effect reported after administration of 60 mg twice daily. Chronic therapy with the 20-mg twice-daily regimen does not lead to a clinical rebound phenomenon, as measured by episodes of angina and nitroglycerin consumption.

The recommended dosage of isosorbide mononitrate is 20 mg twice daily given asymmetrically at 7 A.M. and 3 P.M., i.e., 7 and 17 hours apart. A marginal increase in efficacy may be gained from the use of a 40-mg twice-daily regimen. Doses greater than 40 mg twice daily may be associated with a less favorable safety profile and the development of tolerance, and therefore are not recommended.

Because the development of tolerance precludes continuous nitrate prophylaxis, intermittent therapy represents the only rational strategy for employing nitrates in the management of stable angina pectoris. An intermittent regimen does pose the potential drawback of failing to provide 24-hour antianginal coverage; therefore, some patients may require combination therapy with another class of antianginal agent, such as a β-adrenergic blocker or calcium channel blocker. The combined use of a nitrate and especially a dihydropyridine calcium antagonist must be approached very cautiously, because of the possibility of aggravated hypotension, and should be studied formally.

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DISCUSSION

Dr. William H. Frishman: Has the asymmetrical twice-daily isosorbide mononitrate regimen been compared with an asymmetrical twice-daily dinitrate regimen?

Dr. Philip J. de Vane: A study comparing these 2 regimens has never been conducted. I suspect that the efficacy of the dinitrate would have been improved by asymmetrical dosing but that it would not have matched the performance of the mononitrate, given the variability in absorption, bioavail-

ability, and the need for titration of isosorbide dinitrate.

Dr. Ezra Amsterdam: Another appropriate study might compare the effects of an asymmetrical twice-daily mononitrate regimen with the effects of once-daily therapy with the sustained-release formulation of the dinitrate.

Dr. de Vane: That would be an interesting study. However, a complicating consideration is that the dinitrate is essentially a prodrug, the kinetics of which are subject to many variables. In addition, I am not certain that it is possible to give just a single dose of the long-acting dinitrate and provide acceptable antianginal coverage.

Dr. Jay N. Cohn: About 6 years ago, we demonstrated that the duration of action of a single 40-mg dose of sustained-release isosorbide dinitrate is 8 hours. Second and third doses of the dinitrate do not seem to be valuable if we are concerned about the attenuation of drug effect the following morning.

Participant: This raises the question of what happens during the overnight interval when the patient is not receiving isosorbide dinitrate. Given the compelling clinical evidence of a circadian increase in early morning ischemia and infarction, it might be logical to configure a dosing schedule that provided anti-ischemic coverage in the early morning and a midday nitrate-free interval.

Dr. Udho Thadani: It is not clear that the morning surge in ischemic events necessarily translates into the morning surge in myocardial infarctions. The patients with stable angina pectoris tend to experience angina when they are active and thus primarily require daytime coverage. Patients who experience chest pain upon waking or in the early morning hours often require concomitant therapy with another class of an antianginal medication.

Optimizing Antianginal Therapy: Consensus Guidelines

eading cardiovascular and family medicine specialists who gathered for this consensus conference, "Optimizing Antianginal Therapy," formulated the following guidelines on the treatment of angina pectoris. Intended for use by the practicing physician and in the development of educational programs, these guidelines do not cover all patients with the disease but focus on the typical patient with angina pectoris seen in medical practice today. The topics discussed are treatment of chronic stable and unstable angina pectoris, diagnosis of myocardial ischemia, use of nitrate therapy and concomitant therapies, and recognition and management of nitrate tolerance.

CHRONIC STABLE ANGINA PECTORIS TREATMENT GUIDELINES

MODERATOR: Richard Gorlin, MD, Murray M. Rosenberg Professor of Medicine, Chairman, Department of Medicine, Mount Sinai Medical Center, New York, New York.

Co-Moderator: Harry L. Metcalf, MD, Clinical Professor, Department of Family Medicine, State University of New York at Buffalo School of Medicine, Buffalo, New York.

Clinical presentation: The classic presentation of stable angina pectoris is not one of pain but rather of discomfort, usually but not always originating in the substernal region and radiating to the neck, shoulders, arm, or lower jaw, particularly on the left side. Symptoms may include pressure, burning, a sense of heaviness, dyspnea, faintness, and diaphoresis. Although the discomfort is usually provoked by exercise, emotional stress, or cold and relieved by rest, that pattern of provocation and relief is not always present. Many patients with angina pectoris, particularly older people and women, have an atypical presentation: symptoms may not conform to the classic picture; the provocation and relief pattern may be absent; and the duration of symptoms may vary. Whether classic or atypical, however, any of these clinical symptoms are particularly significant if they occur in conjunction with a family or personal history of hypertension, hyperlipidemia, other cardiovascular disease, diabetes, or tobacco use.

Diagnostic workup: In patients who appear to have chronic stable angina but who also have atypical features, diagnostic tests are done primarily to clarify the diagnosis. In patients with a reasonably typical history and clinical symptoms consistent with the diagnosis of chronic stable angina, such tests help the physician decide what, if anything, should be done about what seems to be the anginal syndrome. For most patients, a physical examination and an electrocardiogram (ECG) provide the first evidence of ischemic, valvular, or hypertensive disease. A symptom-limited exercise stress test is both cost efficient and especially helpful in patients with atypical symptoms or those who are asymptomatic but have multiple risk factors for cardiovascular disease. Provocational imaging testing using adenosine or dipyridamole is an alternative for patients who cannot tolerate an exercise stress test, such as the elderly or people with chronic obstructive pulmonary disease or degenerative joint disease.

Radionuclide or thallium imaging procedures should be reserved for patients whose ECG readings indicate such abnormalities as left ventricular hypertrophy, repolarization disturbances, and left bundle branch block; patients with atypical symptoms and ambiguous ECG readings; and elderly, female, and hypertensive patients, who have a high likelihood of false-positive ECG readings. If the imaging procedure shows multiple zones of reduced perfusion or asynergy, the patient clearly has severe or multiple-system coronary artery disease (CAD).

Coronary angiography is indicated when the exercise stress test demonstrates low aerobic capacity, reduced heart rate response with exercise, hypotension or no increase in blood pressure, early or persistent ST-segment depression (or elevation) over 2 mm, widespread changes on the scalar ECG, and multiple or very large perfusion or contractile defects.

Ambulatory ECG monitoring has no role in the routine evaluation of chronic stable angina.

Coexisting hypertension: The presence of hy-

pertension in patients with suspected ischemic heart disease complicates the diagnostic workup, because different drugs may be indicated from those used for normotensive patients. An echocardiogram is not a routine procedure but may be helpful in certain patients. Because of the high likelihood of a false-positive result from an exercise stress test, an imaging procedure may be needed to establish the presence of coexisting CAD. Severe hypertension should be treated and controlled before an evaluation for CAD is conducted.

Treatment of uncomplicated stable angina: Patients with uncomplicated angina and no markedly positive exercise stress test results should first be treated with medical therapy. The most common regimens are aspirin, antilipid medications if appropriate, long-acting nitrate preparations and/or calcium antagonists, and β blockers. Occasionally, angioplasty may be necessary. Symptomatic patients with markedly positive stress test results should begin aspirin and other medical therapy and be scheduled for coronary angiography. Patients with left main or 3-vessel disease and reduced left ventricular function should undergo surgery; no hard data support the effectiveness of percutaneous transluminal coronary angioplasty in this setting. Treatment of patients with lesions involving 1 or 2 coronary arteries remains unresolved, and the role of medical therapy versus angioplasty versus more extensive surgery is still under evaluation. Treatment of angina complicated by other diseases, such as chronic obstructive pulmonary disease and diabetes, should be individualized. Some patients may benefit from dual therapy with a \(\beta \) blocker and a long-acting nitrate or calcium antagonist.

UNSTABLE ANGINA PECTORIS TREATMENT GUIDELINES

MODERATOR: Peter F. Cohn, MD, Professor of Medicine and Chief of Cardiology, State University of New York Health Sciences Center, Stony Brook, New York.

Clinical presentation: Unstable angina is defined as a new onset of angina or a change in an established anginal pattern (such as the development of angina at rest; more severe, more frequent, or more prolonged episodes; new provocation sources; a different response to medication; nocturnal episodes) or new episodes of angina occurring after myocardial infarction (MI), percutaneous transluminal coronary angioplasty, or coronary ar-

tery bypass graft surgery, especially with ECG changes. The most telling symptom of unstable angina is a *change* in the anginal pattern.

Diagnostic workup: Because it is difficult to make the diagnosis of unstable angina using clinical presentation alone, additional testing may be needed to rule out other cardiac and noncardiac conditions that cause similar symptoms, for example, enzyme testing to rule out MI. Provocational testing, including exercise stress testing, should not be performed until the patient has been stabilized.

Treatment: In initiating treatment, it is essential to take into account other medical problems, such as unsuspected anemia due to chronic blood loss, which can bring on unstable angina, and to consider contraindications to specific drugs such as β blockers in asthmatic patients. All patients with unstable angina initially require general (e.g., oxygen) and medical (e.g., certain drugs) therapy. The medical therapy is aimed at stabilizing the patient and providing long-term management. The treatment algorithm is similar to that for an MI: optimize the myocardial blood supply-demand equation; try to reduce the risk of infarction and death; preserve left ventricular function; and optimize long-term prognosis.

When initiated in the hospital, medical therapy includes early use of multiple anti-ischemic, antiplatelet, and antithrombotic agents. Currently, no evidence supports the use of thrombolytic agents. Once patients are stabilized, the need for revascularization may be determined by exercise stress testing or other appropriate tests.

The response to medical therapy is assessed by control of ischemia at an activity level commensurate with the patient's lifestyle. If patients do not respond clinically and electrographically to medical therapy within a clinically acceptable time period, they should undergo coronary angiography to determine whether angioplasty or a more extensive procedure, such as coronary artery bypass grafting, should be performed. The demonstration of fixed obstructive lesions demands the consideration of surgical or other interventional treatment. Post-MI patients with ongoing angina and patients with unstable angina accompanied by hemodynamic or electrical instability or by widespread ECG changes are at high risk and should be considered for early interventional therapy. Percutaneous transluminal coronary angioplasty should be used to revascularize patients with appropriate clinical features and coronary anatomy.

DIAGNOSIS OF MYOCARDIAL ISCHEMIA

Moderator: Carl J. Pepine, MD, Professor of Medicine, University of Florida College of Medicine, Chief, Cardiology Section, Veterans Affairs Medical Center, Gainesville, Florida.

Co-MODERATOR: Mark Lipkin, Jr., MD, Associate Professor of Clinical Medicine, Director, Primary Care, New York University Medical Center, New York, New York.

Diagnostic tests: Tests should be employed to help support the diagnosis of myocardial ischemia, but the so-called diagnostic tests have a more important role in terms of risk stratification. ECGs, radionuclide perfusion studies, hemodynamic tests, and wall motion studies (conducted with either radionuclide techniques or echocardiography) are useful in documenting functional changes that occur secondary to myocardial ischemia. The 12lead ECG is an almost routine diagnostic test, although all forms of ECG recorded in and about a chest-pain episode are helpful to evaluate patients with known or suspected ischemia. Ambulatory ECG (Holter) monitoring for 24 hours or longer may be employed to evaluate further the patient with proven myocardial ischemia (i.e., coronary artery disease documented by angiogram, positive stress test, or Q-wave myocardial infarction) for the presence of ischemia during daily life activities or the patient with suspected variant angina. Hemodynamic changes are useful in supporting the diagnosis of myocardial ischemia in selected cases, specifically the patient in the coronary care unit with a transient increase in wedge pressure during a symptom episode that is difficult to classify. Chest radiographs, although useful in routine cardiac evaluation, should not be used routinely in the diagnosis of myocardial ischemia; this does not include cardiac fluoroscopy, which can help identify coronary calcification in selected cases.

Coronary angiography: Coronary angiography by itself does not aid in the diagnosis of transient myocardial ischemia per se. It shows the lumen of coronary arteries at only 1 point in time and does not provide functional information about the potential for a given lumen reduction to be responsible for ischemia. Angiography should be performed after functional testing and only when the need for diagnostic and therapeutic decisions outweighs the risks and costs of the test.

Stress tests: The exercise stress test is the single most useful test in the evaluation of patients with either known or suspected myocardial ischemia. Depending on the circumstances, maximal,

submaximal, and target heart rate endpoints can be used. Many exercise protocols are in common use and are adequate for the evaluation of patients with known or suspected myocardial ischemia. For patients who cannot exercise and in other selected cases, alternative stress test methods can be used, including atrial pacing, mental stress testing, and pharmacologic stress testing using adenosine, dipyridamole, or dobutamine. (Not all of these agents are approved by the U.S. FDA for this purpose.)

Because exercise stress tests can be performed frequently and provide objective, semiquantitative data, they are also useful in evaluating treatment results and disease progression. However, the standard Bruce treadmill exercise protocol has limitations in this latter application. Results may also vary depending on treatment choice (i.e., an antiischemic treatment that prolongs exercise time by reducing myocardial oxygen demand would produce results different from those of a treatment that prolongs exercise time by increasing oxygen supply). Other modalities that may be used to evaluate response to antianginal therapy include clinical assessment (angina response), quality-oflife assessment (other findings related to the clinical assessment), ambulatory ECG monitoring, and cardiovascular event rates.

Finally, testing should be done only for the proper indications, using appropriately standardized protocols and equipment calibration, and with due attention to patient safety and test limitations.

NITRATE MONOTHERAPY AND CONCOMITANT THERAPY GUIDELINES

MODERATOR: Jay N. Cohn, MD, Professor of Medicine, Head, Cardiovascular Division, University of Minnesota Medical School, Minneapolis, Minnesota.

Effect of anatomy on treatment choice: The question whether one can use the anatomic distribution of lesions as a guide to pharmacologic intervention, or whether anatomy has little to do with potential responsiveness and therefore should not be taken into consideration, has not been answered definitively. Although the ability of nitrates to reduce proximal coronary artery stenosis may account for some of their benefits, there appears to be a response to nitrates even in the absence of proximal lesions. Syndrome X, for example, manifested by normal coronary epicardial arteries and chest pain, may respond to nitrates. Nonetheless, it is probably prudent to utilize nitrate therapy when moderately tight proximal coronary stenoses threaten myocardial perfusion.

Drugs that dilate arterioles often aggravate myocardial ischemia. Coronary arterioles are not the desirable pharmacologic site of action of an antianginal agent.

Calcium antagonists differ considerably by agent, mechanism of action, and application, with some institutions favoring dihydropyridines and others, diltiazem.

Routes of nitrate administration: Nitrate agents are very safe and, unlike β blockers and calcium antagonists, have essentially no contraindications to their use in patients with angina. Oral administration is probably the most efficacious approach to chronic prophylactic nitrate therapy, although there are indications for sublingual and transdermal therapy. Sublingual therapy is effective in treating symptomatic episodes, but patient compliance may be a problem with prophylactic use.

Concomitant theraples: There is evidence that β blockers prolong survival in post-MI patients, and this might be extrapolated to coronary artery disease in general. This survival-prolonging effect has not been established with other drug therapies, such as nitrates and calcium antagonists, although a well-designed study might prove otherwise for nitrates. Nitrates and calcium antagonists can be given in addition to β -blocker therapy to help relieve ischemia.

Nitrate dosing: A major advantage of isosorbide mononitrate use is that a single dosage appears to be optimal for all patients, eliminating concerns about titration and individual variability. It can be administered twice daily at a set dosage with good bioavailability. Otherwise, there is concern about how to achieve an appropriate dose of an orally effective nitrate. The evidence that a 40 mg dose of mononitrate is less effective than a 20 mg dose puts into question the traditional approach of titrating the dose to maximal toleration.

Side effects: Whether side effects such as headache indicate a generalized vascular effect, including the coronary circulation, is as yet unknown. These issues are poorly understood with isosorbide mononitrate therapy. The dose responses to headache, to the large artery effect, and to the venous effect may all be different.

RECOGNITION AND MANAGEMENT OF NITRATE TOLERANCE

MODERATOR: Uri Elkayam, MD, Professor of Medicine, Chief of Cardiology, University of Southern California (USC) University Hospital, Acting Chief,

Division of Cardiology, USC School of Medicine, Los Angeles, California.

Clinical significance: Because sufficient evidence indicates that tolerance can diminish the antianginal effects of organic nitrates, it should be taken into consideration whenever nitrates are used. However, tolerance may be partial, is not seen in every patient, and is probably dose- and time-dependent. It may also affect some therapeutic endpoints (e.g., hemodynamic changes in patients with heart failure and angina, and exercise-induced ischemia on treadmill) more than others (e.g., silent or symptomatic ischemic episodes occurring during daily activity).

Role of nitrate formulations: On the basis of current data, it appears that tolerance occurs with all long-acting nitrate agents available in the United States, including nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate. Tolerance has not been documented with short-acting nitrate formulations, especially sublingual nitroglycerin.

Mechanism of tolerance: A difference exists between the attenuation of therapeutic effect and tolerance. The most likely mechanism of nitrate tolerance is the depletion of sulfhydryl groups at the cellular level. Attenuation may be related not only to nitrate tolerance, but also to extracellular mechanisms such as activation of neurohormonal vasoconstrictive mechanisms and an early increase in blood volume. Whereas tolerance occurs at the cellular level, attenuation is most likely a multifactorial phenomenon.

Preventing tolerance: Nitrate tolerance can be prevented by several practical methods, including use of a dosing schedule as needed, short-acting nitrate preparations, the lowest effective therapeutic dose, prophylactic short-acting nitroglycerin, and an appropriate nitrate-free interval. In addition, current data suggest that escalating the nitrate dose can temporarily augment its therapeutic effect and thus overcome the initial attenuation.

Dosing regimens: Although dosing data for the various nitrate regimens for the treatment of angina pectoris are incomplete, current dosing schedule recommendations are as follows:

- Oral isosorbide dinitrate, twice or 3 times daily with at least a 12-hour washout period
- Long-acting isosorbide dinitrate, once daily or asymmetrical eccentric dosing twice daily (for example, at 8 A.M. and 3 P.M.).
- Transdermal nitroglycerin, 12 hours on, 12 hours off
- Isosorbide mononitrate, asymmetrical, eccentric dosing twice daily.

Combination therapy: Considering the need for long washout intervals in long-acting nitrate therapy, these agents may need to be used in combination with calcium antagonists or β blockers to prevent ischemic attacks during the nitrate-free intervals.

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A Symposium: Triglycerides as a Vascular Risk Factor: A Global Forum

GUEST EDITORS:

Yechezkiel Stein, MD

Professor of Medicine
Director, Lipid Research Laboratory
Department of Medicine
Hadassah University Hospital
Jerusalem, Israel

Antonio M. Gotto, Jr., MD, DPhil

Chairman, Department of Medicine Baylor College of Medicine Houston, Texas

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Introduction

Yechezkiel Stein, MD, and Antonio M. Gotto, Jr, MD, DPhil

reat progress has been made over the last 3 decades in identifying the most important risk factors for coronary artery disease (CAD), and we have learned to apply measures that successfully lower the incidence of this disease. In the late 1960s, the medical community endorsed and helped implement smoking cessation as a preventive measure against both CAD and lung cancer. In the 1970s, the well-orchestrated campaign against hypertension was begun. In the 1980s, attention was focused on the diagnosis and management of hypercholesterolemia, and this decade also saw the development of potent new cholesterol-lowering drugs.

The declining rates of CAD mortality and morbidity throughout the industrialized world during the same period clearly reflect the identification and proper management of these 3 important risk factors. In the United States, annual CAD mortality rates dropped by about 25% from 1969 to 1983.¹

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Nonetheless, CAD remains the leading killer in the United States and in Europe. In 1989, CAD accounted for the deaths of nearly 1 million U.S. citizens.2 Therefore, the struggle against CAD, including efforts to improve preventive strategies, must continue relentlessly.

One important aspect of current preventive strategies against CAD is the multiple risk factor approach. Yet, widening the net of risk factors increases the complexity of the problem. For example, treatments instituted to improve 1 risk factor can sometimes worsen another, as in the case of some effective antihypertensive agents that raise serum cholesterol levels. How should the physician proceed when multiple risk factors are present in a patient?

One controversial risk factor is hypertriglyceridemia. Many epidemiologic studies have shown a positive correlation between elevated serum triglyceride levels and increased CAD risk, with particularly strong findings in women and patients with non-insulin-dependent diabetes.³ The association remains controversial because of the lack of association in multifactorial analysis, unlike the situation for low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol with



Antonio M. Gotto, Jr., MD, DPhil

CAD. The association demonstrated on univariate analysis often breaks down on multivariate analysis, in particular when HDL cholesterol level is taken into account.3 These findings illustrate the complexity of the CAD-triglyceride relation and suggest that some of the increased risk of CAD in patients with hypertriglyceridemia could be due to reduced levels of HDL cholesterol. Other potentially atherogenic factors associated with hypertriglyceridemia are postprandial lipemia, small dense LDL particles, abnormalities in very-lowdensity lipoprotein, and an increase in coagulation factors.

Nonetheless, in 1987 the Task Force of the European Atherosclerosis Society,4 after prolonged deliberations, came to the conclusion that the putative role of elevated serum triglyceride as an independent causative risk factor for CAD cannot be ignored, for several reasons.

First, the metabolism of triglyceride-rich lipoproteins determines to a great extent levels of HDL cholesterol. This link has been clearly documented in the postprandial state, when the entry of chylomicrons into the circulation challenges the subject's fat-clearing capacity.5,6

Second, several investigators have suggested that extensive postprandial lipemia may induce lipid deposition in arterial cells, 7-10 and thus lead to the development of foam cells.

Third, it has been shown that clearance of LDL particles is affected by their triglyceride content.11 Hypertriglyceridemia is associated with small, dense LDL particles as well as decreased HDL2, representing a highly atherogenic profile.

In the United States, the National Institutes of Health Consensus Development Conference on Triglyceride, High-Density Lipoprotein, and Coronary Heart Disease recently recommended that HDL cholesterol and triglyceride levels be determined to refine CAD risk assessment in a number of patient groups in which such determinations had not been previously suggested by a major U.S.

panel (draft statement issued February 28, 1992). Its outlining of new recommendations for the incorporation of triglyceride level into CAD risk assessment and treatment brings additional major attention to this risk factor and should serve as an impetus to further research.

If in the 1990s we are to revise and broaden successfully our treatment strategies against CAD, we must consider the role of triglyceride management in our multiple risk factor regimens. The speakers enlisted for the symposium "Triglycerides as a Vascular Risk Factor: A Global Forum," brought international expertise to bear not only on the question of a European or United States consensus but on whether a worldwide triglyceride consensus is feasible.

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Epidemiology of Triglycerides: A View from Framingham

William P. Castelli, MD

New analyses from the Framingham Heart Study are presented showing that men and women who have high triglyceride levels (>1.7 mmol/liter) and a low high-density lipoprotein (HDL) level (<1.03 mmol/liter) run a significantly higher rate of coronary artery disease and can be identified, and that this risk group (high triglyceride-low HDL) is, independently of the major risk factors (including low HDL), related to occurrence of coronary artery disease. Further, this trait appears to be common in our society, producing twice as many cases of coronary artery disease during the 14 years of the Framingham study as the next highest disease-producing lipid abnormality. This trait of high triglyceride—low HDL is associated in the medical literature with increased insulin resistance, higher blood sugars (within the normal range), higher uric acid levels, hypertension, and centrally mediated obesity. Because total cholesterol in people with these traits may be less than or just slightly greater than 5.2 mmol/liter, they are missed or neglected by most cholesterol screening programs.

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ontroversy continues about whether abnormal triglyceride levels are a risk factor for coronary artery disease (CAD) or other atherosclerotic vasculopathies. There appears to be little debate about the simple, univariate relation of triglycerides to CAD. In a recent review, Austin¹ described 27 case-control and prospective studies of men in whom it was found that the higher the triglyceride levels, the higher the subsequent rate of some aspect of CAD; this association was significant on univariate statistical analysis. Austin also described several studies of women in whom a significant univariate association of triglycerides with some endpoint of CAD was found.

Many of these 27 studies also showed that the relationship of triglycerides to CAD is significant after controlling for the other major risk factors, such as total cholesterol, low-density lipoprotein (LDL) cholesterol, blood pressure, smoking, and glucose intolerance, but in only a few studies was the relation independent when adjustment was made for high-density lipoprotein (HDL) cholesterol levels. This adjustment for HDL cholesterol has been controversial. On one hand, there are those² who believe that the mathematical model is a good use of statistical modeling; and on the other hand are those³ who point out that, when 2 items are associated both statistically and metabolically, the current mathematical models will grossly underestimate the contribution to risk of 1 of the items, thus representing a misapplication of the statistical

The purpose of this article is to examine new evidence from the Framingham Heart Study as it relates to the triglyceride risk issue. The fundamental problem with using triglyceride levels as a risk factor is that there are 4 kinds of triglyceride, 2 of which are not atherogenic and 2 of which are. Since the techniques used to measure the different kinds of triglyceride-rich lipoprotein particles exist in only a few laboratories in the world, this article will recommend a simple way to estimate the dangerous type of triglyceride, starting with simple clinical measures.

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This article will also describe, for the first time, a triglyceride-rich particle, adjusted by HDL (using stratification) and the other risk factors (using a multivariate analysis), that is independently related to CAD.

METHODS

The Framingham Heart Study was started in 1948. A mostly random sample of 5,209 respondents was selected from the 10,000 men and women in Framingham who were aged 30–60 years. Of the random sample, 5,127 were free of clinically overt disease at entry and formed the prospective cohort. This cohort has been examined biennially for the last 44 years.

The first lipoprotein measurements were made in 1951 in the laboratory of John Gofman⁴ at the University of California in Berkeley. Lipoproteins of Sf 0–12, 12–20, 20–200, and 200–400 were measured in the analytical ultracentrifuge. In the late 1960s, further lipoprotein measurements were made using the beta quantification technique, which was adopted by the Lipid Research Clinics Program⁵ from the initial work of Fredrickson et al.⁶ Cholesterol was measured by the Abell-Kendall method⁷ and triglyceride by the Lederer-Kessler fluorometry method.

The coronary endpoints in the Framingham study included angina pectoris, coronary insufficiency, myocardial infarction, sudden death and nonsudden death from CAD (occurring >1 hour after start of symptoms). The criteria used for these endpoints have been described in the Framingham Monographs and are updated periodically. In brief, angina pectoris is chest discomfort

brought on by exertion or excitement and relieved in 15 minutes, usually 5 minutes, by rest. Myocardial infarction is prolonged chest discomfort associated with electrocardiographic or appropriate enzyme changes, or both. Coronary insufficiency is prolonged chest discomfort associated with transient ST-T wave changes and normal enzyme levels.

The statistical methods have been described in the Monographs and in addition include models related to the Cox proportional hazard models.^{9,10}

RESULTS

In the univariate analysis, the Framingham Heart Study found a simple linear relation between serum triglycerides and the subsequent development of CAD. This was statistically significant in all correlations in women but only in the 30-year data among the men, using the Gofman-determined Sf 20–400 lipoproteins (Figure 1). The correlation was also significant in women after adjustment for the other, most potent and traditional risk factors, such as blood pressure, smoking, and electrocardiographic left ventricular hypertrophy, but not when HDL cholesterol levels were included in the model.

When triglyceride levels were stratified by HDL level, another picture emerges. Figure 2 shows that (triglyceride tertile × HDL tertile) identified 9 subgroups of triglyceride–HDL relations in men. These data are based on triglyceride and HDL cholesterol levels measured 14 years earlier in subjects free of disease who were then followed up for the occurrence of new CAD. Men in the lowest HDL tertile (<1.03 mmol/liter) who were also in

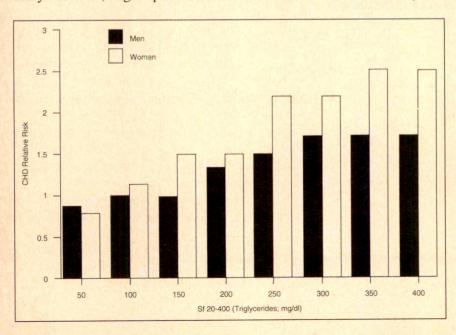


FIGURE 1. Relative risk of coronary artery disease (CHD), by serum triglyceride (Sf 20—400) levels in men and women (30-year follow-up).

Triglycerides (mmol/L) 350 <1.02 1.02-1.57 300 >1.57 250 CHD/1,000/10 Years 200 150 100 50 0 <1.03 1 03-1 27 >1.27 HDL (mmol/L)

FIGURE 2. Incidence of coronary artery disease (CHD), by levels of triglycerides and high-density lipoprotein (HDL) cholesterol in men. *p < 0.05, when adjusted for age, systolic blood pressure, cigarette smoking, body mass index and electrocardiographic left ventricular hypertrophy. Comparisons made in reference to high HDL/low triglyceride group.

the highest triglyceride tertile (>1.57 mmol/liter) experienced the highest rate of CAD; this is significantly different from the lowest risk group and independently adjusted for age, systolic blood pressure, cigarette smoking, body mass index, and electrocardiographically determined left ventricular hypertrophy (p = 0.006; Cox proportional hazard model). Because it stratifies for HDL levels, it is adjusted for HDL as well. Thus, this analysis suggests that there must be a triglyceride-rich

particle related to CAD, independent of the other major risk factors, including HDL.

Figure 2 reveals subgroups of men with very high rates of CAD (high triglyceride-low HDL and low triglyceride-low HDL), but there is another important public health consideration, which is considered in Figure 3. The figure shows that in 14 years there are almost twice as many cases of men with CAD in the high triglyceride-low HDL cholesterol group as in any other group. It should be

Triglycerides (mmol/L)

50 — 1.02
1.02-1.57
>1.57
20 — 10 — 10 — 1.03
1.03-1.27
HDL (mmol/L)

FIGURE 3. Crude incidence of coronary artery disease, number of cases in 14 years, by levels of triglyceride and high-density lipoprotein (HDL) cholesterol in men.

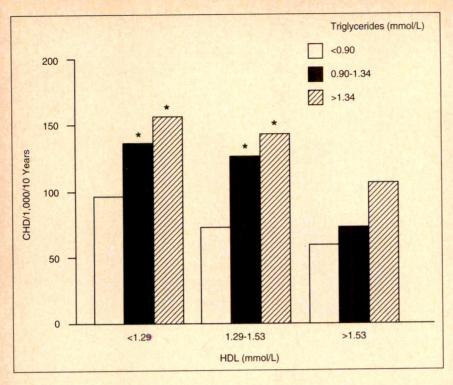


FIGURE 4. Incidence of coronary artery disease (CHD), by levels of triglycerides and high-density lipoprotein (HDL) cholesterol in women. p < 0.05, when adjusted for age, systolic blood pressure, cigarette smoking, body mass index, and electrocardiographic left ventricular hypertrophy. Comparisons made in reference to high HDL/low triglyceride group.

noted how few cases appeared in the low triglyceride—low HDL cholesterol group in Figure 3, the group that had a high rate of disease reported in Figure 2. The difference is the frequency of these traits in our population: one trait is much more frequent and produces a much higher number of cases, in what could be called an attributable risk setting.

The evidence in women is somewhat different. Figure 4 shows the rates of CAD in the 9 subgroups

of triglyceride-HDL cholesterol among women. Unlike the men, an impact of triglyceride tertile on risk can be seen, and also a gradient of risk on tertile of HDL. Again, when adjusted for the most important risk factors, the high triglyceride-low HDL cholesterol subgroup had a highly significant risk of CAD and, due to the stratification on HDL, this independence includes HDL. Figure 5 shows the number of cases produced by the 9 subgroups. Again, 1 group towers over the rest: the high

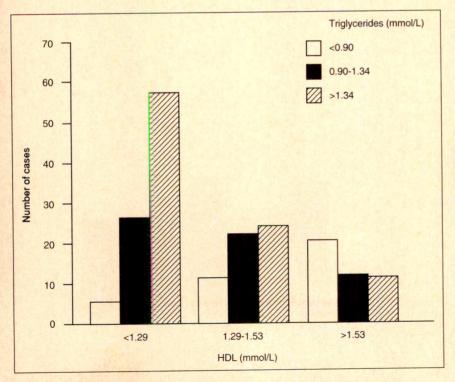


FIGURE 5. Crude incidence of coronary artery disease, number of cases in 14 years, by levels of triglyceride and high-density lipoprotein (HDL) cholesterol in women.

triglyceride-low HDL cholesterol group produced almost twice as many cases as any other group.

DISCUSSION

These data suggest that, in a free-living, healthy population, there is an important high-risk group, identified only by their high triglyceride and low HDL cholesterol levels, who will experience rates of CAD as high or higher than those with more commonly recognized lipid abnormalities. In addition, because high triglyceride-low HDL is such a common lipid disorder in our population, it produces more cases of CAD than familial hypercholesterolemia, the ultimate elevated LDL cholesterol syndrome.

Many persons with high triglyceride-low HDL in our society have total cholesterol levels < 5.2 mmol/liter and average LDL cholesterol levels of about 3.88 mmol/liter. As a result, unless these individuals already have some form of overt atherosclerotic cardiovascular disease or 2 other CAD risk factors, they will be missed by the National Cholesterol Education Program guidelines.

This finding is not peculiar to Framingham. In the Prospective Cardiovascular Münster (PRO-CAM) study conducted in Germany, Assmann and Schulte¹¹ showed that of the first 73 CAD cases in the first 4 years, 37 had a triglyceride level > 1.70 mmol/liter and at the same time their HDL cholesterol levels were < 0.91 mmol/liter. Of the first 500 survivors of myocardial infarction in the Seattle study, 12 of those who were diagnosed hyperlipidemic, 3 times as many had high triglyceride levels as had a simple LDL cholesterol elevation, and the worst cases appeared to have high LDL and high triglyceride levels, the combined hyperlipidemia syndrome. In the Helsinki Heart Study, 13 subjects in the control group with a high LDL:HDL ratio (>5) who also had a high triglyceride level (>2.26 mmol/liter) experienced almost 4 times the heart attack rate in the next 5 years as subjects with just a high LDL:HDL ratio.

Further evidence now suggests that people with high triglyceride and low HDL levels belong to a larger clinical syndrome. High triglyceride levels may lead to insulin resistance, ¹⁴ and Reaven¹⁵ has described a "syndrome X," characterized by high triglyceride and low HDL cholesterol levels, increased insulin resistance, and hypertension. Williams et al¹⁶ called this syndrome "familial dyslipidemic hypertension," showing that it runs in families, accounts for a very high percentage of CAD patients, and is found in 12% of all hypertensive patients in Utah. Kaplan¹⁷ has suggested it begins with centrally mediated obesity that then includes

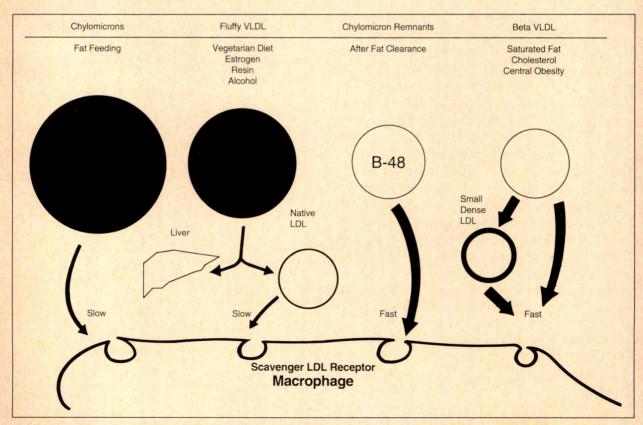


FIGURE 6. The 4 kinds of triglyceride. LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein.

dyslipidemia, insulin resistance, and hypertension, all combining to form the "deadly quartet."

As triglyceride levels increased in the Framingham subjects, both blood glucose and uric acid levels increased, so that their blood sugar levels were in the upper 5% of normal (>5.6 mmol/liter) and their uric acid levels also in the upper 5% (>297 μmol/liter in women, >357 μmol/liter in men).¹⁸

At the metabolic level, the size of the very-lowdensity lipoprotein (VLDL) particle may be paramount in assessing the importance of the triglyceride level. In a study of patients with endogenous hypertriglyceridemia, Poapst et al19 showed that, as the triglyceride levels increased, 75-80% of the triglyceride-rich lipoproteins were in the Sf 12-60 or (intermediate) density class. These particles are very atherogenic, as evidenced by their ultimate expression in type III hyperlipidemias. 20,21 The penultimate expression is in the combined hyperlipidemias in which small dense \u03b3-VLDL particles associated with small dense LDL particles are found. Small dense LDL particles, in hyperapobetalipoproteinemia, have also been incriminated as atherogenic.²² Recently, Austin et al^{23,24} have shown that small dense LDL particles (pattern B) are related to CAD, and these investigators have also given us a better appreciation of its association with triglycerides. In a healthy population, as triglyceride levels increase to 1.13 mmol/liter, small dense LDL particles appear in the plasma and circulating levels of normal, native, larger, less atherogenic (pattern A) LDL decline. When the triglyceride levels reach 1.70 mmol/liter, one is virtually out of the normal pattern of LDL and only the small dense LDL particles are seen. A similar cumulative distribution curve can be drawn using HDL levels. If HDL levels decline to <1.03 mmol/ liter, small dense LDL particles appear and the normal LDL particles disappear. 23,24 This fits nicely with the Framingham results in men and women: when the triglyceride levels reach 1.70 mmol/liter and the HDL level is < 1.03 mmol/liter, a person in the group with high rates of CAD has been found.

At the cellular level, small dense β-VLDL particles are taken up into macrophages or their equivalent at a much higher rate than are native LDL particles to produce foam cells.^{25–27} Some of these small dense β-VLDL particles may appear in the blood after dietary cholesterol ingestion and are taken up into macrophages, exhibiting an atherogenic potential for 2 triglyceride-rich lipoproteins: β-VLDL and chylomicron remnants. One of the controversies surrounding triglyceride is that it

is not supposed to accumulate in lesions. Such statements are probably not true since triglyceride levels increase with age and higher concentrations are found in lesions of diabetic patients than in nondiabetic patients. However, most of the cellular research suggests that the atherogenic triglyceriderich particles increase the deposition of cholesteryl ester; thus, it may be academic whether they also lead to increased triglyceride levels.

Two triglyceride-rich particles are not atherogenic: chylomicrons and normal buoyant VLDL particles of Sf 100-400. A vegetarian diet can produce large, fluffy VLDL particles that are obviously nonatherogenic, since pure vegetarians do not develop atherosclerosis. 28,29 Estrogens produce large VLDL,30 and resins (at least colestipol)31 and alcohol produce a different kind of VLDL that is nonatherogenic. Thus, of the 4 kinds of triglyceride (Figure 6), 2 are not atherogenic and 2 are, which is why a simple schema that considers only triglyceride level is bound to identify people with high triglyceride levels who are not at risk for atherosclerosis. The problem is compounded because there are only a handful of laboratories that can measure the size of VLDL or LDL particles and thus determine the presence of the more or less atherogenic-sized particles.

I propose that these very difficult procedures are unnecessary. All that need be known is that the triglyceride level is > 1.70 mmol/liter and the HDL level is < 1.03 mmol/liter, and that the patient is not a vegetarian. This suggests the presence of the dangerous kind of VLDL and most probably the more dangerous variety of LDL. If the patient's insulin level is also known, it is possible to suggest prospectively that these conditions will be concomitant with blood sugar > 5.6 mmol/liter, uric acid > 357 μmol/liter, a waist to hip circumference ratio > 0.85, an elevated apolipoprotein B level, a total cholesterol:HDL cholesterol ratio > 4.5, and hypertension. In other words, a person who is on the fast track to atherosclerotic vascular disease.

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Role of Triglycerides in Coronary Artery Disease: Lessons from the Prospective Cardiovascular Münster Study

Gerd Assmann, MD, and Helmut Schulte, Dr. rer medic

The incidence of atherosclerotic coronary artery disease (CAD) was assessed in 4,576 male participants of the Prospective Cardiovascular Münster (PROCAM) study, aged 40-64 years, over a 4-year follow-up period. In this time, 122 study participants developed atherosclerotic CAD (89 definite nonfatal myocardial infarctions and 33 definite atherosclerotic CAD deaths). Univariate analysis revealed a significant association between the incidence of atherosclerotic CAD, and high-density lipoprotein (HDL) cholesterol (p < 0.001) and triglyceride (p < 0.01) levels. The relation to HDL cholesterol remained after adjustment for other risk factors. By contrast, the relation between the incidence of atherosclerotic CAD and triglycerides disappeared if, in a multivariate analysis by means of a multiple logistic function, cholesterol or HDL cholesterol was taken into account. However, the data suggested that hypertriglyceridemia is a powerful additional coronary risk factor, when excessive triglycerides coincide with a high ratio (>5.0) of plasma low-density lipoprotein (LDL) cholesterol to HDL cholesterol. Even though the prevalence of this subgroup was only 3.7%, it included a quarter of all atherosclerotic **CAD** events observed.

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n the Prospective Cardiovascular Münster (PROCAM) study, employed subjects (from 52 companies and institutions) were examined for cardiovascular risk factors and then observed for mortality, subsequent myocardial infarctions (MI), and strokes. Clinical history and anthropometric data were taken from each subject at study entry, using standardized questionnaires, blood pressure, a resting electrocardiogram, and a fasting blood sample for assessment of >20 laboratory tests. The examinations were performed in a medical vehicle on the employer's site during paid working hours. Any employee could participate in the study. Participation was voluntary (between 40% and 80% took part; average, 60%) and was free of charge to both the volunteers and their employers (apart from lost working time). Approximately 20 people were examined per day. All findings were reported to each subject's general practitioner. The subjects were told whether the examination results were normal or whether a check-up by a general practitioner was necessary. The study investigators did not arrange for any intervention, leaving this to each subject's general practitioner.

Questionnaires were sent to the participants every 2 years to record any MIs or strokes that had occurred. Notification of any deaths was also required by the registration office of each subject who could not be reached. The participants were told of these questionnaires at study entry, and the response rate was 96% after 2 reminders by either mail or telephone. For every death of a study participant, the death certificate was reviewed. Medical records were obtained, with permission of the patient, for all morbidity factors as gleaned through the questionnaire. The investigators requested hospital records and records from the attending physician to verify the diagnosis, or cause of death, by a critical event committee. Examinations performed at study onset were repeated after 6-7 years.

TABLE I Mean (± SD) Values of Age-Standardized Factors for Men in the PROCAM Study Aged 40-65 Years with (MI+) and without (MI-) Development of Coronary Artery Disease within 4 Years

Variable	MI- (n = 4,352)		MI+ (n = 122)		p Value
Cholesterol (mmol/liter)	5.75	(1.09)	6.47	(1.26)	< 0.001
High-density lipoprotein cholesterol (mmol/liter)	1.16	(0.31)	1.01	(0.25)	< 0.001
Low-density lipoprotein cholesterol (mmol/liter)*	3.81	(0.95)	4.57	(1.10)	< 0.001
Triglycerides (mmol/liter)†	1.51		1.77		< 0.001
Systolic blood pressure (mm Hg)	132.2	(18.7)	138.7	(20.9)	< 0.001
Diastolic blood pressure (mm Hg)	86.1	(11.1)	89.2	(11.9)	0.01
Body mass index (kg/m²)	26.3	(3.0)	26.5	(2.9)	0.44
Number of cigarette smokers	1,473	(33.9%)	72	(59.0%)	< 0.001

I = 4,204 in MI-; I = 117 in MI+

MI = myocardial infarction.

TABLE II Coronary Artery Disease Events (n = 122) in Tertiles of Age-Standardized Factors in the PROCAM Study for Men Aged 10 65 Vears (n - 1 171)

"我们就是我们的一个人,我们就是一个人的,我们就是一个人的。"		CAD Incidence (%) in Tertiles		
Variable	Tertile Cutting Points	Low	Middle	Upper
Cholesterol (mmol/liter)	5.22 and 6.13	1.2	1.8	5.1
High-density lipoprotein cholesterol (mmol/liter)	1.01 and 1.22	5.0	1.8	1.6
Low-density lipoprotein* (mmol/liter) cholesterol	3.36 and 4.19	1.2	1.8	5.1
Triglycerides (mmol/liter)	1.16 and 1.83	1.8	2.7	3.8
Systolic blood pressure (mm Hg)	123 and 138	1.9	2.1	3.8
Body mass index (kg/m²)	24.9 and 27.2	2.3	2.7	3.2

The PROCAM study began in 1979 and the recruitment phase was completed at the end of 1985. There are full data records for a total of 19,698 participants. The participants' were aged 16-65 years. The average age and standard deviation of the 13,737 men was 41.4 ± 11.2 years; the 5,961 women had a distinctly lower age of 36.6 ± 12.5 years.

For the following analysis, 2 endpoints were considered: MI and death due to coronary artery disease (CAD), including sudden and nonsudden death.

INCIDENCE OF CAD ACCORDING TO **HIGH-DENSITY LIPOPROTEIN CHOLESTEROL** AND TRIGLYCERIDES

Because adequate numbers of subjects with MI or dying of CAD in the PROCAM study occurred only in men aged ≥40 years, the analysis to be described was confined to 4,576 male participants aged 40-65 years, without a prior history of MI or stroke. Follow-up was for 4 years.

In this group of 4,576 subjects, 122 experienced MIs or fatal CAD (MI+ group; 33 CAD deaths and 89 MI), 87 men died from causes other than CAD, and 15 nonfatal strokes were observed.

Thus, 4,352 subjects survived the 4 years after the examination without MI or stroke (MI- group). The age-standardized mean values of risk factors within the groups MI+ and MI- are shown in Table I. The numbers of observed CAD events per tertile of relevant variables are shown in Table II.

High-density lipoprotein (HDL) cholesterol levels < 0.9 mmol/liter were found in 50.0% of the MI+ subjects and in 17.0% of the MI- subjects. Further, 21.2% of the MI- group and 39.3% of the MI+ group had triglyceride levels ≥ 2.3 mmol/ liter. In logistic function analyses, HDL cholesterol (p < 0.001) and log-transformed values of triglycerides (p < 0.01) showed a significant association with the incidence of CAD. Although the relation with HDL cholesterol remained after adjustment for other risk factors, the relation with triglycerides disappeared when cholesterol or HDL cholesterol was accounted for in a multivariate analysis (multiple logistic function).

By contrast, hypertriglyceridemia (≥ 2.3 mmol/ liter) was associated with a markedly higher incidence of CAD in subjects categorized by levels of cholesterol (Figure 1), HDL cholesterol (Figure 2), and low-density lipoprotein (LDL) cholesterol (Figure 3). In the groups with LDL cholesterol levels of

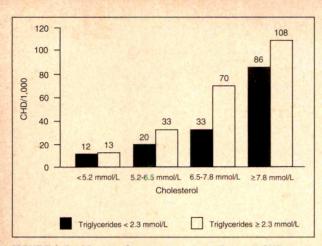


FIGURE 1. Incidence of coronary artery disease (CHD; per 1,000 in 4 years) according to levels of triglycerides and cholesterol.

4.1–4.9 mmol/liter and > 4.9 mmol/liter, hypertriglyceridemia tripled CAD rates. Further, the participants with high LDL:HDL cholesterol ratios (>5.0; 11.2% of the men) showed a markedly higher risk of CAD (99/1,000 subjects in 4 years) than the men with ratios < 5.0 (18/1,000 subjects in)4 years). In both groups, CAD rates were higher in hypertriglyceridemic subjects (Figure 4). In particular, the hypertriglyceridemic subjects with high LDL:HDL cholesterol ratios exhibited the highest risk of CAD. Even though only 3.7% of the men

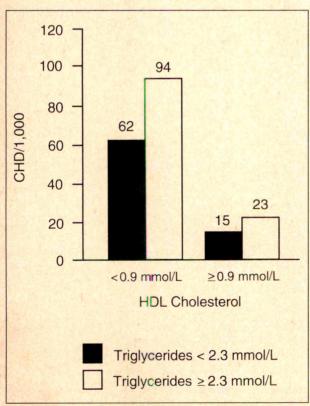


FIGURE 2. Incidence of coronary artery disease (CHD; per 1,000 in 4 years) according to levels of triglycerides and high-density lipoprotein (HDL) cholesterol.

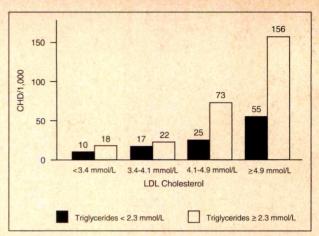


FIGURE 3. Incidence of coronary artery disease (CHD; per 1,000 in 4 years) according to levels of triglycerides and low-density lipoprotein (LDL) cholesterol.

were in this group, they comprised nearly 25% of all CAD incidences observed.

Among the hypertriglyceridemic men with high LDL:HDL cholesterol ratios, 17.8% had diabetes mellitus or elevated fasting blood glucose (>6.67 mmol/liter) and 45.6% were hypertensive (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥ 95 mm Hg). Among the remainder, 8.4% had elevated blood glucose levels and 30.4% were hypertensive. Further, the subgroup of PROCAM participants with an elevated cholester-

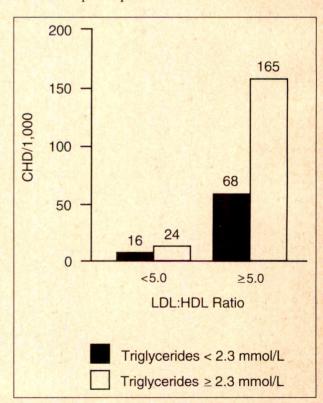


FIGURE 4. Incidence of coronary artery disease (CHD; per 1,000 in 4 years) according to triglyceride levels and the low-density lipoprotein:high-density lipoprotein (LDL:HDL) cholesterol ratio.

ol:HDL cholesterol ratio (>5.0) in conjunction with low HDL cholesterol levels (<0.9 mmol/liter) showed an increased risk if triglyceride levels were elevated (9.5% vs 6.0%).^{2,3}

Strong support, underscoring the importance of the triad of high triglycerides, low HDL cholesterol, and elevated LDL cholesterol, is provided by recent analysis of the Helsinki Heart Study. 4.5 Patients in this subgroup with triglyceride levels > 2.3 mmol/liter and an LDL:HDL cholesterol ratio > 5.0 had by far the highest incidence of cardiac events (130/1,000 in the placebo group). Treating patients in this subgroup was particulary effective, reducing the incidence of cardiac events by > 70%. Comprising 10% of the trial population, these patients represented about 50% of the CAD events saved by gemfibrozil.

CONCLUSION

Taken together, the data from the PROCAM study and the Helsinki Heart Study suggest that the hypertriglyceridemia/low HDL cholesterol syndrome constitutes a powerful risk factor for nonfatal MI or CAD death that would escape attention if

LDL cholesterol levels alone were determined. Apparently, when high triglyceride concentrations (>2.3 mmol/liter) coincide with a high ratio of plasma LDL cholesterol to HDL cholesterol (>5.0), steps should be taken to normalize the lipid profile. For practical purposes, it appears advisable to base any risk prediction for atherosclerotic CAD as well as any treatment decision on a full lipid profile (cholesterol, triglycerides, LDL cholesterol, HDL cholesterol) rather than total and/or LDL cholesterol determinations alone.

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Triglyceride Levels and the Risk of Coronary Artery Disease: A View from Australia

Leon A. Simons, MD

A prospective study of cardiovascular disease in elderly Australians commenced in 1988 in Dubbo, **New South Wales. The study population com**prised 1,237 men and 1,568 women aged ≥60 years. The prevalence rates of coronary artery disease (CAD) and putative risk factors were examined cross-sectionally in the baseline data. The age-standardized rate of CAD was 23.8/100 men and 18.1/100 women. In a univariate analysis, the major risk factors for CAD were hypertension, diabetes, family history, reduced high-density lipoprotein (HDL) cholesterol levels, and increased triglyceride levels. The prevalence rate of CAD was examined in those with low-density lipoprotein (LDL):HDL ratios <5.0 or >5.0. Most notably in women, the CAD rate was 16/100 with an LDL:HDL ratio ≤5.0 and 28/100 with an LDL: HDL ratio >5.0. In the latter group, the rate was 21/100 in those with triglycerides ≤2.3 mmol/ liter and 36/100 in those with triglycerides > 2.3 mmol/liter. In a multiple logistic model that controlled for many potential risk factors or confounding variables, CAD in men was significantly predicted by age, hypertension (odds ratio = 1.40), family history (odds ratio = 2.05), and low HDL cholesterol (odds ratio = 0.78). Significant predictors in women were age, years of education (odds ratio = 0.82), hypertension (odds ratio = 1.45), family history (odds ratio = 1.77), serum triglycerides (odds ratio = 1.30), and low HDL cholesterol (odds ratio = 0.73). An independent gradient of CAD risk with increasing triglyceride levels and a similar gradient with decreasing HDL cholesterol levels were found in women.

When HDL cholesterol was <0.91 mmol/liter, the odds ratio for CAD was 5.37 when triglyceride levels were >2.24 mmol/liter. The findings with respect to triglyceride levels in women and HDL cholesterol in both sexes are important for future risk-factor management. Confirmation of the data, however, is needed from longitudinal studies.

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otal mortality and that from coronary artery disease (CAD) and stroke have been declining in Australia since 1970. These declining rates have been observed in both sexes, in those dying < 65 years, and in those dying in older age (Figure 1). Combined with a decreasing birth rate, this explains the gradual aging of the Australian and other populations. The reasons for decreasing cardiovascular mortality rates in the elderly require study.

Risk factors for CAD appear to be well known, including hypertension, cigarette smoking, lipid disorders, diabetes, and a family history of CAD. However, this information is derived from predominantly middle-aged populations. Data on risk factors in the elderly are fragmentary and often contradictory. With respect to lipid disorders, total serum cholesterol does not appear to be a strong predictor of CAD in the elderly,²⁻⁴ although some studies contradict this view.5-7 A reduced highdensity lipoprotein (HDL) cholesterol level can predict future CAD in the elderly.^{8–10} Triglyceride and CAD data in the elderly are sparse, but a few reports have suggested significant prediction of CAD by increasing triglyceride levels. 10,11

This conflicting information was the background for a new prospective study of cardiovascular diseases in elderly Australians that commenced in Dubbo, New South Wales, in 1988.¹² Clinical, biochemical, and sociologic data at baseline were recently documented.¹³ This article will review the results of cross-sectional analysis of CAD and its risk factors as ascertained at study entry.

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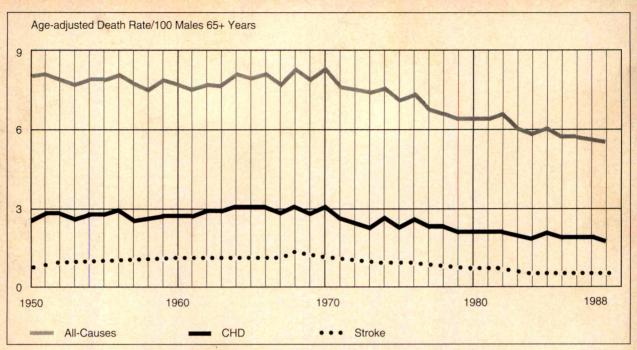


FIGURE 1. Mortality rates in Australia, 1950-1988, for men ≥ 65 years, CHD = coronary artery disease.

METHODS

The study population comprised all noninstitutionalized residents of Dubbo who were born before January 1, 1930 (i.e., those ≥ 60 years) and who were assessed at study entry (1,237 men and 1,568 women). Examinations occurred over a 13month period starting in August 1988. The attendance rate was 73% (2,805 of 3,860) and declined slightly with age. The medical examination included anthropometry, blood pressure, and resting electrocardiography. A standardized questionnaire covered items such as alcohol and tobacco use, vears of education, medical history, use of medications, family history of CAD, and any physical or other activities. Rose angina and myocardial infarction questionnaires were also administered, and 12-hour fasting venous blood was collected for

estimation of total cholesterol and triglycerides, HDL cholesterol, and plasma glucose. Prevalence of CAD at study entry was assessed from the myocardial infarction questionnaire, definitive electrocardiographic changes, or from the angina questionnaire. Univariate and multivariate analyses were performed with a multiple logistic model to assess the independent predictors of CAD. Full details of the methods used have recently been published.14

RESULTS

The sex- and age-specific prevalence rates for CAD are presented in Figure 2. The rate increased with age until 79 years in men and then declined. The rate increased steadily with age in women, exceeding the male rate in the years ≥ 80 . The

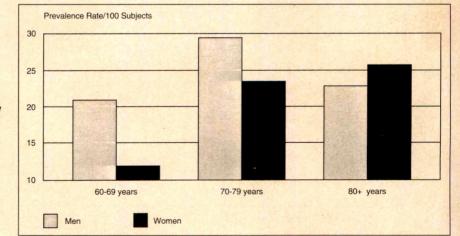


FIGURE 2. Prevalence of coronary artery disease in Dubbo, New South Wales, by age and sex.

	M	en	Wor	men
	CAD	No CAD	CAD	No CAD
Number	295	844	274	1,200
Cholesterol	6.06 ± 1.24	6.16 ± 1.17	6.94 ± 1.32	6.81 ± 1.22
LDL cholesterol	3.99 ± 1.14	4.09 ± 1.01	4.66 ± 1.19	4.61 ± 1.11
Triglycerides	1.98 ± 1.79	1.75 ± 1.20	2.12 ± 1.41	1.63 ± 0.82
HDL cholesterol	1.17 ± 0.31	1.24 ± 0.34	1.30 ± 0.39	1.48 ± 0.39

age-standardized rate of CAD was 23.8/100 men and 18.1/100 women.

Compared with subjects free of CAD, in univariate analysis male subjects with CAD were older; more likely to have smoked; more often hypertensive, diabetic, or with a stronger family history of CAD; and were slightly less educated. Women with CAD were older; not as likely to have smoked; more often hypertensive, diabetic, or with a stronger family history of CAD; and less educated than women without CAD. The lipid results are summarized in Table I. CAD subjects had similar total and LDL cholesterol levels compared with subjects free of CAD. However, triglycerides were higher and HDL cholesterol was lower in CAD subjects. In further univariate analysis, CAD rate was recalculated by the LDL:HDL ratio (<5.0 or >5.0) and by fasting triglyceride level (<2.3 or >2.3 mmol/ liter). (Figure 3 presents results for women and Figure 4, for men.) The prevalence of CAD was always greater in the group with an LDL:HDL ratio > 5.0, particularly in women. The prevalence of CAD was greater in women with triglyceride levels > 2.3 mmol/liter than in those with triglycerides ≤ 2.3 mmol/liter, independent of the LDL: HDL ratio. These relations with triglycerides were not clearly present in the men. However, the data are potentially confounded by a differential pres-

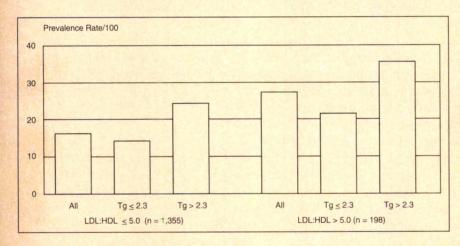


FIGURE 3. Coronary artery disease rates in women based on triglyceride (Tg) levels and lowdensity lipoprotein:high-density lipoprotein (LDL:HDL) ratios.

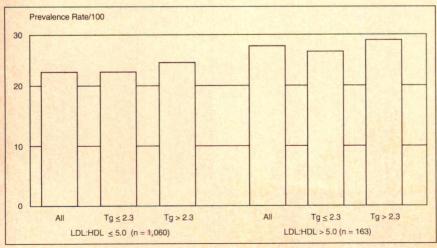


FIGURE 4. Coronary artery disease rates in men based on triglyceride (Tg) levels and low-density lipoprotein:high-density lipoprotein (LDL:HDL) ratios.

ence of diabetes and hypertension in the various triglyceride subgroupings.

Ultimately, all risk factors and potentially confounding variables were introduced into a multiple logistic model to study the independent prediction of CAD. Family history of CAD, hypertension, triglycerides (women only), HDL cholesterol and years of education (women only) were the significant predictors of CAD (Table II). Since the distribution of serum triglycerides was skewed, we arbitrarily grouped triglycerides into 3 categories: <1.60, 1.60–2.24, and >2.24 mmol/liter. HDL cholesterol was also arbitrarily grouped into 3 categories: <0.91, 0.91-1.19, and >1.19 mmol/ liter. The multivariate logistic models were then recalculated, replacing the continuous variables by dummy variables representing the upper 2 triglyceride groupings and the lower 2 HDL groupings. The approximate relative risk of CAD by triglyceride and HDL grouping is shown for women in Figure 5 and for men in Figure 6. In each instance, the reference group included subjects with triglycerides < 1.60 mmol/liter and HDL-cholesterol > 1.19 mmol/liter. With respect to HDL cholesterol in both sexes, a graded relation was clearly shown with CAD risk, independent of triglycerides and all other variables in the model. Increasing triglyceride levels were associated with an increasing risk of CAD in a graded fashion in the women only. The

TABLE II Significant Predictors of Coronary Artery Disease (CAD) in Multiple Logistic Regression

	Males		F	Females	
	Odds Ratio	CI	Odds Ratio	CI	
Family history of CAD	2.05	1.52-2.77	1.77	1.32-2.36	
Hypertension	1.40	1.05-1.88	1.45	1.03-2.05	
Triglycerides	NS		1.30	1.10-1.52	
HDL cholesterol	0.78	0.65-0.92	0.73	0.61-0.89	
Years of education	NS		0.82	0.70-0.95	

effects of triglycerides and HDL were independent, and the magnitude of excess risk was greatest in those from the lowest HDL cholesterol and highest triglyceride groupings (odds ratio = 5.37). As anticipated, there was no consistent relation between increasing triglyceride levels and CAD risk in men.

DISCUSSION

Our goal was to predict the risk of developing CAD in a large and essentially representative sample of elderly citizens of a semi-urban Australian township. However, the findings are based on prevalence rather than incidence data for CAD. In such a retrospective examination it was impossible to rely on the standard criteria for myocardial

FIGURE 5. The estimated relative risk of coronary artery disease in women based on triglyceride levels and high-density lipoprotein (HDL) cholesterol concentrations. (Reprinted with permission from J Am Geriatr Soc.14)

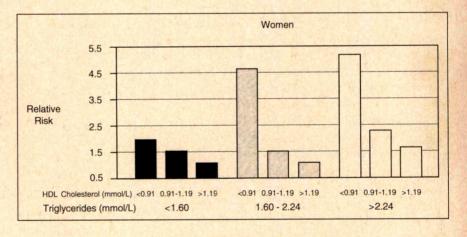
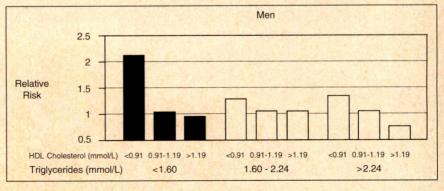


FIGURE 6. The estimated relative risk of coronary artery disease in men based on triglyceride levels and high-density lipoprotein (HDL) cholesterol concentrations. (Reprinted with permission from J Am Geriatr Soc. 14)



infarction used in longitudinal studies. The criteria for CAD were partially historical and were potentially subject to recall bias. In addition, we only examined "survivors" with CAD. Risk factors may have differed in nonsurvivors, and the survivors may have made certain life-style adjustments. Finally, we experienced a slight recruitment bias in favor of younger subjects. Although these factors may conceivably conceal true risk-factor relations, interesting and relevant etiologic relations can be generated in cross-sectional data.

The prediction of CAD based on serum triglyceride levels has been controversial. The Framingham Heart Study¹⁰ demonstrated in longitudinal data that serum triglycerides are predictive of CAD in women ≥ 50 years, but not in men, when other variables are controlled, and that this risk increased still further with a reduced concentration of HDL cholesterol. We virtually replicated these findings but in subjects ≥ 60 years. In Dubbo women, the risk of CAD increased in a graded fashion, as did the serum triglyceride concentration (Figure 5). When HDL cholesterol was < 0.91 mmol/liter, the odds ratio for manifesting CAD was 2.18 for triglycerides < 1.60 mmol/liter, 4.85 for triglycerides 1.60–2.24 mmol/liter, and 5.37 for triglycerides > 2.24 mmol/liter. This was relative to women with triglycerides < 1.60 mmol/liter but with HDL > 1.19 mmol/liter in a multiple logistic model. HDL cholesterol is an independent risk factor for CAD in both sexes, whereas triglycerides are an independent risk factor in women only. Although these findings may be important for further risk factor intervention, confirmation is needed from our ongoing longitudinal study.

Total serum cholesterol consistently failed to predict the presence of CAD in either sex. This was not surprising, given the lack of consistency in earlier prospective studies²⁻⁷ and the inherent difficulties acknowledged above in a retrospective cross-sectional study. Further, numerous studies11,15,16 have indicated a J-shaped relation between total cholesterol and all-causes mortality. The absence of lipid-intervention data in the elderly and a fear of possible adverse outcomes has

generally dictated a conservative approach.¹⁷ Future prospective results from this study may clarify the relation between total cholesterol and CAD risk.

Acknowledgment: We express our appreciation to the following coinvestigators of the Dubbo Study: John McCallum (Canberra), Judith Simons (Sydney), and Yechiel Friedlander (Jerusalem). The study received financial support from the National Health and Medical Research Council of Australia and the National Heart Foundation of Australia.

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Hypertriglyceridemia: Risks and Perspectives

Antonio M. Gotto, Jr. MD. DPhil

The evidence linking hypertriglyceridemia and coronary artery disease (CAD) is reviewed. A positive correlation between plasma triglyceride level and CAD incidence has been demonstrated in most prospective studies on univariate analysis. However, the significance is weakened on multivariate analysis, in particular when level of highdensity lipoprotein (HDL) cholesterol is taken into account, perhaps because of the close metabolic interrelation between the triglyceride-rich lipoproteins and HDL particles. Recent analyses of clinical data have shown that the combination of elevations of low-density lipoprotein cholesterol and triglyceride and low levels of HDL cholesterol confers particularly high risk for CAD. The U.S. **National Institutes of Health Consensus Develop**ment Conference on Triglyceride, High Density Lipoprotein, and Coronary Heart Disease in February 1992 made recommendations to integrate more fully HDL cholesterol and triglyceride levels into the assessment and treatment of dyslipidemia and CAD risk. Treatment of hypertriglyceridemia should focus on diet and weight control, exercise, and smoking cessation, as well as control of other major risk factors for CAD, notably hypercholesterolemia and hypertension.

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The prognostic value of plasma triglyceride concentration for the development of coronary artery disease remains controversial. Nearly all case-control studies have shown a significant positive correlation between triglyceride level and coronary artery disease incidence. The relation is confirmed in most prospective studies on univariate analysis, but on multivariate analysis of their data it weakens or disappears, in particular when high-density lipoprotein (HDL) cholesterol level is taken into account.^{1,2} Recently, however, the validity of analyzing triglyceride predictivity against HDL cholesterol predictivity has been questioned because of the close metabolic interrelation of the triglyceride-rich lipoproteins and HDL particles.³

METABOLIC INTERRELATIONS

Dietary (exogenous) triglyceride is transported as part of chylomicrons (Figure 1, bottom). These large particles are synthesized in the intestine and also incorporate cholesteryl esters, phospholipids, apolipoprotein (apo) B-48, and possibly apo A-I. Apo C-II and apo E must be added to the chylomicron (either in the lymph or in the circulation) to enable, respectively, hydrolysis of the lipoprotein's triglyceride component via lipoprotein lipase activity and effective binding of the lipoprotein to hepatic receptors for its removal. Hydrolysis of the chylomicron's triglyceride yields the smaller chylomicron remnant, a particle thought to be atherogenic⁴ that is rapidly removed by the liver. The isoform of apo E present on chylomicron remnants in part determines their rate of removal via the receptors. For example, remnants that contain apo E_2 are removed more slowly than those containing apo E₃ or apo E_{4.5} Recent findings by Beisiegel et al⁶ suggest that in addition to catalyzing the hydrolysis of the triglyceride component of chylomicrons, lipoprotein lipase facilitates binding of the remnants to the hepatic receptor. Other recent evidence has suggested that the apo E remnant receptor in the liver is identical to a primitive receptor that recognizes activated α₂-macroglobulin.⁷

Very-low-density lipoprotein (VLDL) is synthesized and secreted by the liver in the endogenous

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pathway of lipid metabolism (Figure 1, top).8 The triglyceride component of VLDL is also attacked by lipoprotein lipase, to yield the intermediatedensity lipoprotein, a remnant particle. As with chylomicron remnants, there is evidence that intermediate-density lipoproteins are atherogenic.4 VLDL remnants are heterogeneous: some contain apo E, whereas others perhaps do not; there certainly is heterogeneity in size. The larger particles are removed more rapidly. A substantial portion of the VLDL remnants are removed from the circulation through binding to the low-density lipoprotein (LDL) receptor (also called the B/E receptor) in the liver. In humans, a significant portion of the VLDL remnants are converted to LDL particles, most likely through the action of hepatic lipase. As hepatic LDL receptor activity decreases, the proportion of intermediate-density lipoproteins converted to LDL particles would increase. Of the LDL particles formed, it is thought that approximately 80% are removed via the B/E receptor, with the other 20% removed in peripheral tissues by so-called low-affinity pathways.9

As mentioned above, the metabolism of HDL¹⁰ is intimately related to that of the triglyceride-rich lipoproteins. Nascent, discoid HDL particles are

secreted by the intestine and liver, and possibly by macrophages, and they mature into spherical HDL as they add surface components from the triglyceride-rich lipoproteins (e.g., chylomicrons, VLDL) during the hydrolysis of the latter. The surface components—apolipoproteins, phospholipids, and unesterified cholesterol from the triglyceride-rich lipoproteins—are added to the small HDL3 particles. In addition, these particles may obtain cholesterol by interacting with cell membranes, a process possibly facilitated by apo A-I, apo A-II, or apo A-IV. Once within the HDL particle, the cholesterol is converted to cholesteryl ester through the action of lecithin:cholesterol acyltransferase. Generation of cholesteryl esters by the lecithin: cholesterol acyltransferase reaction leads to enlargement of the small HDL₃ particles, so that they are converted into the larger HDL₂ particles. Formation of HDL2 increases the cholesterolcarrying capacity of HDL, and HDL cholesterol levels increase, driving the hypothesized process termed reverse cholesterol transport, in which HDL returns cholesterol from peripheral tissues to the liver for excretion. The interconversions of HDL are summarized in Figure 2.11 Data from Castro and Fielding, 12 and others, suggest that a pre-β-

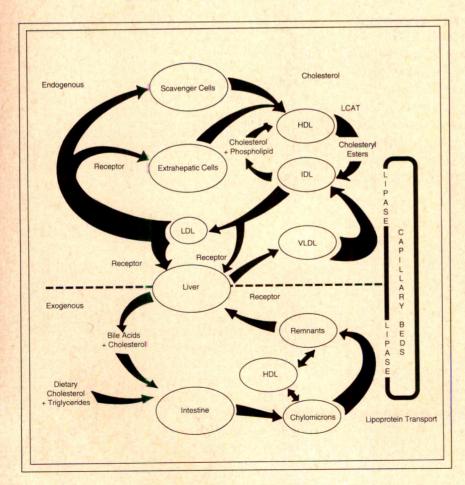
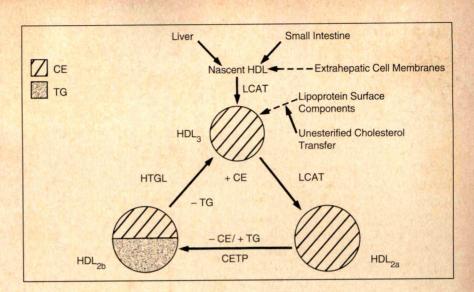


FIGURE 1. Simplified schematic of the endogenous (very-low-density lipoprotein [VLDL]) and exogenous (chylomicron) metabolic pathways of lipid transport.

HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LCAT = lecithin:cholesterol acyltransferase; LDL = low-density lipoprotein. (Reprinted with permission from Stanbury et al.⁸)

FIGURE 2. Interconversions of high-density lipoprotein (HDL) subfractions. CE = cholesteryl ester; CETP = cholesteryl ester transfer protein; HTGL = hepatic (triglyceride) lipase; LCAT = lecithin:cholesterol acyltransferase; TG = triglyceride. (Reprinted with permission from Postgrad Med.11)



migrating HDL particle containing only apo A-I plays an important role in reverse cholesterol

The cholesteryl esters of HDL, particularly of HDL2 formed by lecithin:cholesterol acyltransferase action, 13 need not remain within the HDL core. They can be transferred from HDL particles to the triglyceride-rich lipoproteins in exchange for triglyceride molecules. This exchange of insoluble cholesteryl esters and triglycerides between HDL and the triglyceride-rich lipoproteins is mediated by the action of cholesteryl ester transfer protein. 14-16 The transferred triglycerides are hydrolyzed from the HDL core by hepatic lipase¹⁷ from the endothelial cells of the liver. Only cholesteryl esters remain in the HDL core. Hence, HDL2 particles are converted back into the small HDL₃ particles. 18 Conversion to HDL3 occurs preferentially with HDL2 particles that contain both apo A-I and apo A-II, as opposed to apo A-I alone, because of enhanced interaction with hepatic lipase. 19,20 When the rate of clearance of triglyceride-enriched remnants is decreased, exchange of cholesteryl ester from HDL into the remnants increases. It is well established clinically that patients with permanent or temporary hypertriglyceridemia (due to increased levels of VLDL or accumulation of chylomicrons in the course of postprandial lipemia) tend to have low HDL2 and low HDL cholesterol levels. Since the transferred cholesteryl esters remain with the triglyceride-rich lipoproteins along their lipolytic cascade and the endocytotic pathways of their remnants (e.g., the LDL-receptor and the scavenger pathways), the heteroexchange may contribute to the atherogenic potential of chylomicrons and VLDL, in that "good" cholesterol is turned into "bad" cholesterol.²¹ The formation of small, dense LDL particles, low HDL cholesterol concentration, thrombogenesis, increased postprandial lipoproteins, and the formation of large VLDL all may accompany hypertriglyceridemia (Figure 3).22

RISK FACTOR CLUSTERING

Austin et al²³ used gradient gel electrophoresis to identify 2 major LDL subclasses. In persons with LDL pattern A (or phenotype A), the large, buoyant LDL particles predominate; in pattern (phenotype) B, small, dense LDL particles predominate. Pattern B is associated with increases in plasma triglyceride and apo B levels and decreases in HDL cholesterol and apo A-I, and with a 3-fold increased risk of myocardial infarction.24 Austin et al^{25,26} have described phenotype B as occurring in as much as 30% of the population, inherited as an autosomal dominant trait with reduced penetrance in premenopausal women and in males aged < 20. Others have questioned whether the LDL sub-

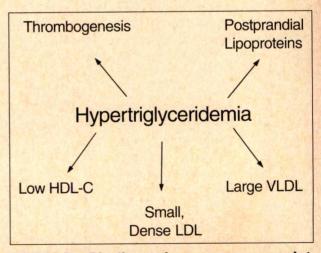


FIGURE 3. Possible atherogenic processes accompanying hypertriglyceridemia. HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein; VLDL = verylow-density lipoprotein. (Reprinted with permission from Arch Intern Med.22)

classes may not be more genetically heterogeneous. Interestingly, LDL phenotype B can occur with a plasma triglyceride level as low as 2.6 mmol/liter.

Apo B-rich, dense LDL is also an aspect of hyperapobetalipoproteinemia (hyper-apo B), as are a high apo B content in VLDL, a relative decrease in HDL cholesterol concentration (particularly of HDL₂), and increases in intermediatedensity lipoproteins, triglycerides, and coronary artery disease risk.27-29 "Syndrome X," described by Reaven, 30,31 may tie together several entities, including LDL phenotype B, the hyper-apo B syndrome, familial dyslipidemic hypertension,³² and hypertriglyceridemia. Reaven postulates a primary underlying defect of resistance to insulin-stimulated glucose uptake with hyperinsulinemia. Syndrome X may involve not only the aforementioned increase in VLDL triglyceride, decrease in HDL cholesterol, and increase in dense LDL constituency, but also hypertension. Whether there is 1 entity with different modes of expression or several entities is not known. Familial combined hyperlipidemia^{33,34} entails many of the same metabolic disturbances.

RECENT CLINICAL FINDINGS

It is of interest that in recently published data from the Physicians' Health Study,35 higher levels of total HDL, HDL₂, HDL₃, and HDL without apo A-II were all found to correlate significantly with reduced risk of myocardial infarction, but that HDL₃ had the strongest correlation among these. Analyses were of blood samples collected prospectively for this aspirin/β-carotene trial (enrollment of 14,916 male physicians): 246 subjects with confirmed new myocardial infarction versus 246 control subjects matched for age, smoking status, and time since randomization. Franceschini et al³⁶ postulated that defective regeneration of HDL_{3c} particles is involved in the development of atherosclerosis and coronary artery disease. An increase in hepatic lipase activity could account, at least in part, for this phenomenon.

Other evidence for the atherogenicity of triglyceride-rich particles comes from the Cholesterol-Lowering Atherosclerosis Study, a randomized, placebo-controlled angiographic trial of colestipol plus nicotinic acid in men who had undergone coronary bypass surgery. In this trial, the best predictor of atherosclerotic lesion nonprogression in the drug-treated group was increased apo C-III content in HDL.³⁷ A high apo C-III level is an indicator of a rapid rate of catabolism of HDL₃.

Further, in the Helsinki Heart Study,³⁸ a 5-year randomized coronary primary prevention trial among dyslipidemic middle-aged men (mostly with type IIa but about 30% with type IIb and 10% with type IV hyperlipoproteinemia), the patients who benefited most from treatment with gemfibrozil in reduction of coronary artery disease incidence were those who had type IIb hyperlipoproteinemia, i.e., increased levels of both LDL cholesterol and triglyceride (and relatively low levels of HDL cholesterol). The main effect of gemfibrozil is to increase HDL₃ concentrations.

In the controlled but nonblinded 5-year Stockholm Ischaemic Heart Disease Secondary Prevention Study,³⁹ conducted among myocardial infarction survivors, it was among the subjects with hypertriglyceridemia that the study's combined clofibrate and nicotinic acid achieved significant reductions in coronary and all-cause mortality rates. It should be noted that 50% of the study's subjects had hypertriglyceridemia, whereas only 13% had hypercholesterolemia.

TREATMENT ALGORITHMS

Triglyceride level does not enter into the primary algorithm of the current National Cholesterol Education Program adult diagnosis and treatment guidelines. The algorithm is structured chiefly around total cholesterol level, LDL cholesterol level, and the presence of other (nontriglyceride) cardiovascular risk factors or existing coronary artery disease. The 1988 National Cholesterol Education Program guidelines recommend that hypertriglyceridemia be treated if the level exceeds 11.29 mmol/liter, to protect against pancreatitis. In contrast, the European Atherosclerosis Society guidelines of the same year consider triglyceride level in addition to total cholesterol level and other risk factors in stratifying risk.

The most recent recommendations from the National Institutes of Health on the diagnosis and treatment of hypertriglyceridemia (and low HDL cholesterol) come from its Consensus Development Conference on Triglyceride, High Density Lipoprotein, and Coronary Heart Disease held February 26–28, 1992.⁴² These recommendations are those of a conference panel and thus do not bear the weight of the National Cholesterol Education Program algorithm; they seek to supplement rather than replace the program's 1988 guidelines. Recommendations on serum triglyceride in relation to cardiovascular risk had last been issued by a National Institutes of Health consensus panel in 1983.⁴³

In its extensive review of a wide range of preclinical and clinical data, the 1992 panel found considerable evidence for a causal relation between HDL and coronary artery disease but mixed data regarding the possible causal role of triglyceride in this disease. It recommended that American physicians incorporate HDL cholesterol measurement into routine screening for coronary artery disease if accuracy of measurement, appropriate counseling, and follow-up can be assured. Further, it delineated additional clinical circumstances under which HDL cholesterol and triglyceride should be measured—among them, in known coronary artery disease, in the setting of a desirable total cholesterol level (<5.17 mmol/liter) when ≥ 2 coronary heart disease risk factors are present, and in such disorders as diabetes mellitus and hypertension (Table I). Its definitions of low HDL cholesterol and hypertriglyceridemia (Table II) did not vary from those of the 1983 consensus conference and the 1988 National Cholesterol Education Program guidelines.

The panel recommended treatment (Table III) for borderline hypertriglyceridemia occurring with a low HDL cholesterol level and a desirable LDL cholesterol level (≤ 3.36 mmol/liter), and for distinct hypertriglyceridemia, with hygienic measures (weight loss, diet, exercise, and smoking cessation) being the mainstay of therapy in all cases. It emphasized that HDL cholesterol and triglyceride values cannot be interpreted in the absence of information about LDL cholesterol. No consensus was reached for drug therapy in the former category of patients, but the panel noted that it may be considered in unusual cases when hygienic measures fail and coronary artery disease or a strong risk profile is present. For the latter category, the panel concluded that drug therapy is warranted to reduce the risk of pancreatitis if hygienic measures fail, and that drugs should be considered as initial therapy with hygienic measures if a history of pancreatitis is present.

The 1992 National Institutes of Health Consensus Development Conference had been preceded by a 3-year study of triglyceride as a risk factor for coronary artery disease by the International Committee for the Evaluation of Hypertriglyceridemia as a Vascular Risk Factor,44 which concluded that the scientific basis for relating hypertriglyceridemia to coronary artery disease risk is weaker than that existing for LDL cholesterol elevation. The report of the International Committee endorsed the National Cholesterol Education Program guidelines and concurred that the major focus should be TABLE I Additional Lipid Measurements Recommended by the 1992 NIH Consensus Development Conference on Triglyceride, High Density Linoprotein and Coronary Heart Disease

High Density Lipoprotein, and Co	oronary Heart Disease"
Measure HDL-C (nonfasting sample	acceptable)
Healthy in <mark>di</mark> viduals	In addition to TC to assess CAD risk if accuracy of HDL-C measurement and appropriate counseling and follow-up can be assured
Measure HDL-C and TG (fasting sai	mple), given†:
Known CAD	To access risks for progression of CAD and development of additional cardiovascular complications
Increased TC	To identify patients with high HDL-C and desirable LDL-C levels as at low-to-average lipid risk for CAD‡
Desirable TC $+ \ge 2$ risk factors§	To identify patients with low HDL-C and/or high TG, as at possible additional risk for CAD
Other disorders that may be associated with increased TG and known to be associated with increased CAD risk, including diabetes, peripheral vascular disease, hypertension, central obesity, chronic renal disease	To refine CAD risk assessment
Lactescent serum, lipemia retinalis, xanthomas, pan- creatitis	To identify familial hyperlip- idemic disorders and/or likeli- hood of recurrence of pancre- atitis; to follow response to treatment

HDL-C *Data from NIH 42

On hygienic or drug therapy

for high TG and/or low

To follow results of therapy

*It is generally recommended that at least 2 (ideally 3) samples be taken at least 1 week apart before a treatment decision is finalized.

‡Under NCEP adult guidelines, ⁴⁰ lipoprotein analysis is performed if there is high TC, or borderline-high TC and ≥2 other risk factors, to identify patients with increased

LDL-C. §The 1992 NIH panel noted that accumulating evidence suggests that postmeno-pausal status be considered an additional risk factor for CAD. CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NCEP = National Cholesterol Education Program; NIH = U.S. National Institutes of Health; TC = total cholesterol; TG = triglyceride. Reprinted with permission from Curr Opin Cardiol.⁴⁹

TABLE II Definitions of High TG and Low HDL-C in Plasma by the NIH Consensus Development Conference on Triglyceride, High Density Lipoprotein, and Coronary Heart Disease⁴²

Lipid Value	Dyslipidemia	Comment
TG 2.82-5.64	Borderline	No change from 1983
mmol/liter	hypertriglyceridemia	NIH consensus ⁴³
TG > 5.64 mmol/	Distinct	No change from 1983
liter	hypertriglyceridemia	NIH consensus ⁴³
HDL-C < 0.905 mmol/liter	Low HDL-C	Same cutpoint as in 1988 NCEP adult guidelines. ⁴⁰ Considered very high risk; cutpoint may be too low for women and certain other sub- populations

HDL-C = high-density lipoprotein cholesterol; NCEP = National Chole Education Program; NIH = U.S. National Institutes of Health; TG = triglyceride.

TABLE III Treatment Recommendations of the 1992 NIH Consensus Development Conference on Triglyceride, High Density Lipenratain and Caranany Heart Disease*t

Density Lipoprotein, and Corona	ry Heart Disease*†
Lipid Values‡	Treatment§
Borderline HTG or low HDL-C (regardless of total cholesterol)	Hygienic measures should al- ways be instituted
Borderline HTG + low HDL-C + desirable LDL-C	Hygienic measures. No consensus for the use of drug therapy, but may be considered in unusual cases when hygienic measures fail and CAD or strong risk profile is present
Distinct HTG	Hygienic measures are initial therapy. If hygienic measures fail, drug therapy is warranted to reduce the risk of pancreatitis. Drugs should be considered as initial therapy with hygienic measures if history of pancreatitis is present
Special Cases	
Very low or absent HDL-C + desirable LDL-C + distinct HTG	Probably represents rare genetic disorders, which require ex- pert evaluation; no specific therapy
Primary hypoalphalipoprotein- emia; low HDL-C; TG and	Hygienic measures and control of coexisting risk factors for

*Data from NIH.4

range

*Data from NIH. *2

†TG and HDL-C cannot be interpreted in the absence of LDL-C. The NIH panel is in general agreement with the 1988 NCEP adult guidelines⁴0 that LDL-C ≥ 4.14 mmol/liter refractory to hygienic therapy may require drug therapy; considerations in the decision include presence of CAD or other risk factors (perhaps to include postmenopausal status). Current data indicate that triglyceride concentrations may contribute to risk assessment and should be considered in making therapeutic

CAD. Drugs that ordinarily

ineffectual

increase HDL-C levels may be

contribute to risk assessment and should be considered in making therapeutic decisions.

‡HTG and low HDL-C are defined in Table II. Desirable LDL-C is ≤3.36 mmol/liter as established in the 1988 NCEP adult guidelines.⁴⁰
§Beyond the clinical situations listed here, there is no consensus for treating isolated mild, sporadic HTG and/or low HDL-C with drugs in the general population.

CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; HTG = hypertriglyceridemia; LDL-C = low-density lipoprotein cholesterol; NCEP = National Cholesterol Education Program; NIH = U.S. National Institutes of Health; TG = triglyceride.

Adapted from Curr Opin Cardiol.⁴⁹

LDL-C usually in desirable

on LDL cholesterol. Nonetheless, there is new evidence from the Prospective Cardiovascular Münster (PROCAM) study^{45,46} and from the Helsinki Heart Study⁴⁷ that persons with elevations of both LDL cholesterol and triglyceride and low levels of HDL cholesterol are at higher risk for coronary artery disease than persons with elevation of LDL alone.

Thus, the International Committee's diagnosis and treatment suggestions for hypertriglyceridemia⁴⁸ are stratified not only by triglyceride level, but also by LDL cholesterol level, the presence of additional risk factors, and the presence of additional disease. Isolated moderate hypertriglyceridemia is defined by a triglyceride value of 2.26-4.52 mmol/liter. Persons with such hypertriglyceridemia plus elevated LDL cholesterol (>3.36 mmol/ liter) are considered to be at very high risk. Finally, an average triglyceride value > 4.52 mmol/liter is considered to constitute severe hypertriglyceridemia.

The International Committee⁴⁸ recommends that treatment of hypertriglyceridemia be considered on an individual basis. Treatment in most cases should focus on diagnosis and control of underlying diseases and on diet and other nonpharmacologic interventions, including stopping cigarette smoking, increasing physical activity, and restricting alcohol consumption. When LDL cholesterol is elevated, the primary focus should be on treating that elevation. The use of a drug for treating hypertriglyceridemia alone is controversial and is not part of the recommendations of the International Committee. Except for defining borderline hypertriglyceridemia as 6.47 versus 5.17 mmol/ liter, the recommendations of the National Institutes of Health Consensus Development Conference and those of the International Committee are quite similar.

CONCLUSION

The relation between plasma triglyceride level and coronary artery disease is very complex, in particular because of the close metabolic interrelation of the triglyceride-rich lipoproteins and HDL. Triglyceride level in patients with existing coronary artery disease, a strong family history of coronary artery disease, diabetes mellitus, renal failure, familial combined hyperlipidemia, or low HDL should receive special attention from the physician. When LDL cholesterol is low and triglyceride is elevated, a major interventional effort should be made.

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Therapeutic Management of Triglycerides: An International Perspective

Thomas A. Pearson, MD, PhD

Current recommendations from various international expert committees generally concur in their definitions of borderline and high triglyceride levels, with small but important differences between recommendations in the definition of normal levels. However, population-based data on triglyceride levels are poorly developed in most countries, making difficult any international comparisons of prevalences of hypertriglyceridemia using the new definitions. However, it is probable that there should be considerable differences in the prevalence of hypertriglyceridemia, probably due to a mixture of genetic and environmental influences. The management of hypertriglyceridemia must continue to emphasize the detection and correction of secondary causes, even though the specific secondary causes may vary between countries. Dietary and exercise interventions must deal with local customs and resources, including striking international differences in alcohol consumption. Pharmacologic therapies will likely increase in use if they follow the trends in countries with available data. Although various drugs are available, nicotinic acid and fibric acid derivatives remain the drugs of choice. Considerably more research is needed to describe these international differences in etiology, prevalence and management practices of hypertriglyceridemia.

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he increasingly recognized role of triglyceride-rich lipoproteins in atherogenesis has led to new recommendations for identification and management of elevated serum triglycerides, including new, lower action limits for fasting triglyceride levels. 1-7 These new recommendations, put forth by a panel of international experts from the lipid metabolism field, are potentially useful to physicians of all countries where atherosclerotic disease is the main cause of mortality. The impact of these recommendations, however, will differ from country to country, just as current recommendations for hypertriglyceridemia treatment differ among countries. Further, the magnitude of atherosclerotic risk posed by elevated triglycerides may vary among nations because of differences in gene frequencies and environmental exposures. Management of hypertriglyceridemia may also vary because of differences in secondary causes, local dietary customs, and limited availability of triglyceride-lowering drugs. These and other related issues are the focus of this review.

CURRENT RECOMMENDATIONS REGARDING DEFINITIONS AND TREATMENT OF HYPERTRIGLYCERIDEMIA

During the mid-to-late 1980s, expert committees were convened from various professional groups interested in hyperlipidemia and atherosclerosis prevention to recommend definitions and management plans for hypertriglyceridemia.²⁻⁶ Some committees discussed only hypertriglyceridemia²; others discussed all lipid disorders, including those dealing with triglycerides.³⁻⁶ Their recommendations for the definition of borderline and high triglyceride levels are consistent (Table I), with a rather narrow range of triglyceride levels used for definition of normal and high. Most also identified the risk of pancreatitis at even higher levels, although this varied from committee to committee.

Although the range of definitions of normal triglyceride levels is small, these minimal changes in cutpoints translate into large differences in prevalence of borderline levels, given the distribu-

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tion of triglycerides in the typical European or North American population. For example, the difference in prevalence of "abnormal" triglyceride levels using a cutpoint of >2.3 mmol/liter versus that of >2.8 mmol/liter in 40-59-year old U.S. white males would be approximately 20% versus 10%, respectively (Figure 1).8 Changing the cutpoint for high triglycerides from 5.6 to 4.5 mmol/liter would have a relatively smaller impact on the number of persons entering treatment.

Most recommendations emphasized examining triglyceride levels in the context of the entire lipid profile, including low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels. Although dietary therapies were consistently advocated, enthusiasm for drug therapy varied considerably.

INTERNATIONAL DIFFERENCES IN THE PREVALENCE OF HYPERTRIGLYCERIDEMIA

There are few data about the prevalence of hypertriglyceridemia in various countries. In many large international studies, serum triglycerides were not routinely obtained or fasting samples were not required.9 Moreover, the association of triglyceride levels to age and gender would require the careful matching of comparison groups (Figure 2). The prevalence of hypertriglyceridemia in white males obviously increases dramatically in middle age. However, the likelihood that there would be substantial differences in the prevalences of hypertriglyceridemia between countries is great, since comparisons of subgroups even within a country show substantial differences. For example, blacks in the United States have lower serum triglyceride levels than whites, especially men (Table II).8 Thus, substantially more white males than other race and sex groups would be identified as borderline or high by the newly proposed definition of hypertriglyceridemia.

Genetic hypertriglyceridemias: Several genetic forms of hypertriglyceridemias have been identified (Table III). ¹⁰ At least 2 of these disorders, familial combined hyperlipidemia ¹¹ and familial dyslipidemic hypertension, ¹² are common, each affecting $\geq 15\%$ of patients with coronary artery disease or hypertension.

Specific gene polymorphisms have been linked to several of these disorders; most have not been described at the molecular level. Polymorphisms of apoprotein E are a good example of the genetic basis for a hyperlipidemia (i.e., remnant hyperlipidemia) that might have considerable international, interracial, and interethnic variations (Table IV). The E2 polymorphism varies at least 2-fold, obvi-

TABLE I Definitions of Normal, Borderline, and High Fasting Serum Triglyceride Levels: Recommendations of Various Expert Panels

	Serum Triglycerides (mmol/liter)			
Expert Committee	Normal (no therapy)	Borderline (diet)	High (drug therapy possible*)	
U.S. Consensus Conference, 1984 ²	<2.9	2.8–5.6	> 5.6	
European Atherosclerosis Society, 1987 ^{3,4}	<2.3	2.3–5.6	> 5.6	
British Hyperlipidaemia Association, 1987 ⁵	<3.0	3.0-6.0	>6.0	
Canadian Consensus Conference, 1988 ⁵ †	<2.3	≥2.3		
International Committee, 1991 ⁷	<2.3	2.3–4.5	>4.5	
*After failure of diet. †For adults > 30 years of age.				

ously affecting the prevalence of remnant hyperlipidemia and possibly other lipid disorders. Other genetic hypertriglyceridemias, although unstudied, might contribute to an increased prevalence of elevated triglycerides in specific populations.

Acquired hypertriglyceridemias: Numerous factors, including metabolic conditions, dietary constituents, and therapeutic drug regimens, have been identified as potential causes of elevated

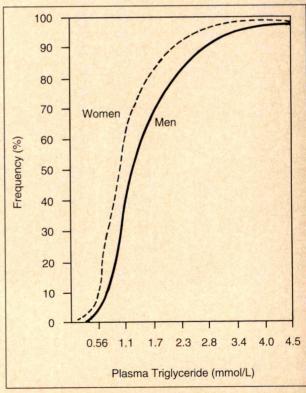


FIGURE 1. Cumulative frequencies of fasting plasma triglyceride levels in white men and women, aged 40–59 years, in the Lipid Research Clinics Prevalence Study (Visit 1). (Reprinted with permission from the Lipid Research Clinics.8)

TABLE II Mean and 90th Percentiles for Fasting Plasma
Triglyceride Levels in Middle-Aged Whites Versus Blacks in the
Lipid Research Clinics Prevalence Study of North America
(Visit 1)

and the st		Plasma Triglycerides (mmol/liter)				
			Men	W	/omen	
Age (yr)	Race	Mean	90th Percentile	Mean	90th Percentile	
30-34	Whites	1.4	2.4	1.0	1.6	
30–39	Blacks	1.2	1.9	0.9	1.5	
40-44	Whites	1.7	2.8	1.2	1.9	
40-49	Blacks	1.4	2.4	1.1	1.7	
Reprinted v	vith permissio	n from the L	pid Research Clir	nics.8		

TABLE III Primary (Genetic) Focus of Hypertriglyceridemia

Chylomicronemia (type I)

Type V hyperlipoproteinemia

Hepatic triglyceride lipase deficiency

Remnant hyperlipidemia (type III)

Familial hypertriglyceridemia

Familial combined hyperlipidemia

Hypertriglyceridemia in high-density lipoprotein deficiency

Familial dyslipidemic hypertension

Reprinted with permission from Assmann and Brewer. 10

TABLE IV Apoprotein E (Apo E) Allele Frequencies and Mean Cholesterol Levels in 3 Populations

	Finland	Germany	Japan
Mean cholesterol (mmol/liter)	5.6	4.8	4.6
Apo E allele frequency			
E-2	0.04	0.08	0.04
E-3	0.73	0.77	0.85
E-4	0.23	0.15	0.11

serum triglyceride levels (Table V). Many are common, with known variations between countries. For example, the prevalence of obesity varies markedly from country to country. A male with a body mass index of 28 kg/m² is at the 90th percentile in Beijing but at the 50th percentile in Kaunas, Lithuania. Thus, the increased prevalence of obesity in certain regions might be logically expected to predispose those populations to hypertriglyceridemia. Similarly, populations prone to diabetes might be predicted to have higher prevalences of elevated triglyceride levels.

A country's national diet, including alcoholic beverage consumption, is often an important definition of the culture. However, the amount of fat (especially saturated fat) contributes to both obesity and hypertriglyceridemia. The international variation in the amount and sources of fat is considerable, suggesting that societies with high fat consumption may have higher triglyceride levels (Figure 3). Conversely, societies in which most of the fat comes from fish might be expected to have low triglyceride levels.

Few dietary constituents vary as much as alcohol consumption.¹⁴ The relation of alcohol to serum triglycerides has been well described and may constitute a gene–environment interaction in some persons.¹⁵ Thus we might expect to find lower triglyceride levels in Norway than in France, with its 24-fold higher wine consumption.

Finally, various pharmacologic agents, including β blockers, thiazides, and retinoids, affect serum triglyceride levels. Female sex hormones, specifically estrogens (Table VI),⁸ are the most widely used agents with potent triglyceride effects. The

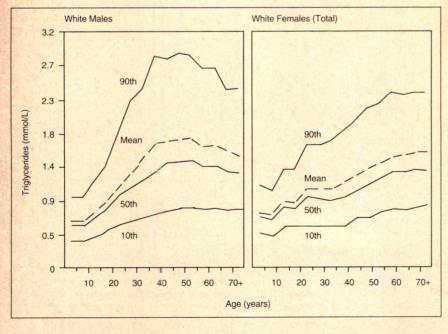


FIGURE 2. Means and selected percentiles of fasting plasma triglyceride levels in white males and females by age in the Lipid Research Clinics Prevalence Study (Visit 1). (Adapted with permission from the Lipid Research Clinics.8)

prevalence of triglyceride levels > 2.3 mmol/liter in women using sex hormones exceeds 10% at ages > 40 years, whereas these levels are much less common in nonusers. Of course, postmenopausal estrogen use has been associated with a 30–50% reduction in coronary risk. Although these triglyceride elevations would not be associated with risk, they would still be identified in any screening program involving serum triglyceride levels.

CURRENT THERAPEUTIC MANAGEMENT OF TRIGLYCERIDES

Treatment of secondary causes: The first step in the management of hypertriglyceridemia is the identification and correction of secondary causes (Table V). Just as the prevalence of diabetes, hypothyroidism, nephrotic syndrome, renal failure, and paraproteinemias differs between countries, the prioritization of testing may also change. However, consideration of all these causes and simple testing for these conditions should be standard practice in all countries.

Nonpharmacologic therapy: Attaining ideal body weight is the cornerstone of nonpharmacologic therapy for hypertriglyceridemia. Obviously, the high prevalence of obesity in some societies may tax even the most well-equipped health care system, particularly since weight management is often characterized by high labor input and high failure rates. Nonetheless, caloric restrictions—especially restriction of fat and simple sugars—should be universally recommended. However, a program of safe physical activity to accelerate caloric expenditure is also necessary. The availability of nutritional counseling services and the necessity for physical activity influences how easily obesity can be controlled.

Reducing saturated fat input is recommended as part of a prudent diet and will affect triglyceride levels. Again, local dietary customs and each na-

Metabolic conditions	
Diabetes mellitus	Nephrotic syndrome
Obesity	Renal failure
Hypothyroidism	Paraproteinemias
Dietary factors	
Fat and saturated fat	
Simple sugars	
Alcohol	
Drugs	
Estrogens	Retinoids
Beta blockers	Thiazides

TABLE VI Fasting Plasma Triglyceride Levels in White Women Using Sex Hormones Versus White Women Not Using Sex Hormones

	Plasma Triglycerides (mmol/liter)					
		Users		onusers		
Age (yr)	Mean	90th Percentile	Mean	90th Percentile		
20-24	1.2	1.7	0.8	1.3		
30-34	1.3	2.0	0.9	1.4		
40-44	1.5	2.3	1.1	1.7		
50-54	1.5	2.3	1.3	2.1		
60-64	1.4	2.2	1.4	2.3		

tion's agricultural sector will influence the availability of sources high in saturated fat. Likewise, the availability of fish high in omega-3 fatty acids will influence triglyceride levels, both as a substitute for foods high in saturated fat and as a foodstuff with direct triglyceride-lowering properties.

Finally, controlling alcohol consumption may be easier in some countries than others, depending on the role of wine and beer as daily beverages in some countries versus their role as social beverages in other countries.

Pharmacologic therapy: Nicotinic acid and fibric acid derivatives remain the drugs of choice for hypertriglyceridemia. Various forms of niacin

FIGURE 3. Trends from selected countries in the consumption of animal and vegetable fats between 1961 and 1985 in grams consumed per person per day. (Reprinted with permission from Int J Epidemiol. 14)

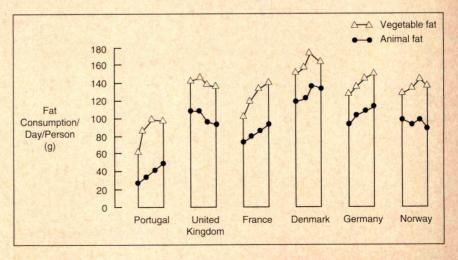


TABLE VII Use of Lipid-Lowering Medications in Patient Days per 100 People per Year and Compounded Growth Rates per Year in 8 Selected Countries*

Country	Patient Days/100 People		Compounded Growth Rate/Year
	1983	1987	1983–1987
Belgium	99.69	163.72	+13
Canada	29.01	40.02	+8
France	653.49	929.42	+9
West Germany	193.94	357.22	+16
Italy	138.29	295.28	+21
Spain	74.42	140.81	+17
United Kingdom	13.15	18.09	+8
United States	25.66	72.34	+30

*Patient—day estimates, which were provided by Warner-Lambert Company, were derived from underlying market research data provided by 2 market research firms. These firms gave permission to Warner-Lambert Company to make these derived data available for the purpose of this study.

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are available; it is unknown whether the regular form of niacin versus the slow-release form is used preferentially in specific countries. Various fibric acid derivatives are available; gemfibrozil is the dominant form in the U.S. market. Bezafibrate, gemfibrozil, fenofibrate, and ciprofibrate are used in Europe and other regions; clofibrate is another fibric acid derivative. Bezafibrate, fenofibrate, and ciprofibrate appear to have greater LDL cholesterol-lowering effects than gemfibrozil, but their role in the management of hypertriglyceridemia is less well defined. 16 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors apparently are modestly effective in mixed hyperlipidemias¹⁷ but not in pure hypertriglyceridemias. Fish oil supplements should not be considered as primary drug therapy for hypertriglyceridemia but may be used in daily doses of 12-20 g as adjunct therapy in cases resistant to other agents.

Considerable differences exist between countries in their use of lipid-lowering medications (Table VII).18 For example, France has a 12-fold higher usage of these agents than the United States. Unfortunately, the agents prescribed and their indications are unknown. However, these differences in levels of prescription may be due partly to differences in prevalence of hyperlipidemias, including hypertriglyceridemia. The magnitude of the differences suggests that local standards of medical practice are also a contributing

The United States is undergoing a dynamic change in the use of lipid-lowering medications. The rate of increased use of these agents in the United States exceeds most other Western countries (Table VII). The overall increase in prescription use has been accompanied by changes in the specific agents prescribed (Figure 4).¹⁹ Clofibrate dominated the U.S. market in 1978 with 81% of prescriptions, until the World Health Organization Collaborative Trial,²⁰ which reported increased mortality in the clofibrate group, led to a drop in its popularity.

Gemfibrozil, however, has greatly increased in use since its introduction in 1982, buoyed by the findings of the Helsinki Heart Study²¹ of its safety and efficacy in reducing cardiac events. The third triglyceride-lowering drug, nicotinic acid, has moderately increased in use, plateauing at a current 8% of prescriptions (not including over-the-counter sales).

Few international data are available on the current prescribing practices for the specific indication of hypertriglyceridemia. A recent survey of prescriptions written in the United States suggests that gemfibrozil is prescribed in almost 80% of the cases of pure hypertriglyceridemia treated with drugs (Table VIII; International Marketing Services, New York, New York, unpublished data). Interestingly, approximately 14% of these cases are prescribed lovastatin, which is not considered a

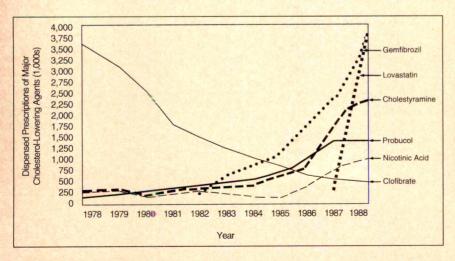


FIGURE 4. Estimated number of dispensed prescriptions of major cholesterol-lowering medications for 1978 through 1988 in the United States based on the National Prescription Audit. (Reprinted with permission from JAMA. 19)

TABLE VIII Drugs Prescribed for Hypertriglyceridemia and for Other Hyperlipidemias in a Survey of United States Pharmacies, March—April 1991

Drug	Hypertriglyceridemia (n = 351) (%)	Other Hyperlipidemias (n = 3,747) (%)
Niacin	5.1	5.9
Slo-Niacin	0.1	0.4
Lovastatin	14.2	35.7
Gemfibrozil	78.1	41.7
Resin	0	10.7
Probucol	2.0	5.6

first-line drug for this condition. Noteworthy is the 10-fold difference in the number of prescriptions written for other hyperlipidemias. Presumably this consists largely of cases of combined hyperlipidemia and probably reflects the high prevalence of combined hyperlipidemia relative to other lipid disorders. In this category, the leading agents are gemfibrozil and lovastatin, with approximately 42% and 36% of prescriptions, respectively. Niacin constitutes only 5–6%, which almost certainly represents an underestimation because niacin is available over the counter.

CONCLUSION

Current recommendations from various international expert committees generally concur in their definitions of borderline and high triglyceride levels, with small but important differences between recommendations in the definition of normal levels. However, population-based data on triglyceride levels are poorly developed in most countries, making difficult any international comparisons of prevalences of hypertriglyceridemia using the new definitions. Thus, the impact of the new recommendations is difficult to gauge on a country-by-country basis. However, it is probable that there should be considerable differences in the prevalence of hypertriglyceridemia, probably due to a mixture of genetic and environmental influences. The management of hypertriglyceridemia must continue to emphasize the detection and correction of secondary causes, even though the specific secondary causes may vary between countries. Dietary and exercise interventions must deal with local customs and resources, including striking international differences in alcohol consumption. Pharmacologic therapies will likely increase in use if they follow the trends in countries with available data. Although various drugs are available, nicotinic acid

and fibric acid derivatives remain the drugs of choice. Considerably more research is needed to describe these international differences in etiology, prevalence, and management practices of hypertriglyceridemia. A worldwide consensus in the definition, detection, and treatment of hypertriglyceridemia would be a major step in refocusing our attention on this potentially important risk factor.

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